Dementia and Motor Neuron Disease

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Foreword

This book reflects the growing interest in the strength and nature of the association of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) and it is a timely summary of the burgeoning research in the field. The papers were presented in the First International Research Workshop on Frontotemporal Dementia in ALS in London, Ontario, a year ago and the volume appears relatively quickly after the conference; a tribute to the editor and organizers and the authors of course who contributed promptly.

Sporadic reports of this association appeared even before the last 45 years but the remarkable number of endemic ALS and dementia was discovered in Guam as Arthur Hudson summarizes it in his introductory chapter. The topic is reviewed in further detail by Daniel Perl. Pathologists knew of course that the upper motor neurone is involved in the cortex since Charcot, but ALS was not considered to affect the mind. Arthur Hudson wrote a much quoted article in Brain in 1981 about what was known of the association of ALS Parkinsonism and dementia up until then, but it was not until the Japanese authors, particularly Mitsuyama and others published several clinical series that the extent of this association began to be appreciated. The nature of the cognitive impairment was not really specified until Neary et al described FTD and MND and Caselli progressive aphasia and MND, and both the behaviour and the language component of FTD/Pick complex became definitely associated with ALS, beyond other cognitive impairment detected on neuropsychological examination.

Once you look, you begin to find, and both the ALS and FTD researchers unearthed a spectrum of abnormalities. Now the search is on in several directions. Since the availability of ubiquitin staining, pathologists found MND type inclusions, previously considered typical in the spinal cord of ALS patients, in frontal association cortex in a large number of cases. In fact it appears in the majority of FTD autopsies even without clinical ALS. The former entity of dementia lacking distinctive histology (DLDH) underlying many FTD cases is rapidly disappearing, since most of them turn out to have these distinctive enough ubiquitin positive, tau and synuclein negative inclusions. ALS researchers emboldened by the FTD groups describing ALS patients in 7–10 % of their cohorts systematically found FTD and nonspecific cognitive impairment in a fair portion of their populations. ALS patients are ill, anxious and depressed, not an ideal group to do systematic cognitive testing. Yet the numbers affected are large, even though the extent and nature of deficit is variable, depending on what is being tested.

The terminology is not getting simpler. Many authors attempt to rename entities, sometimes to clarify, sometimes to innovate. What was MND-type Inclusion (MNDI) becomes FTD-U. FTD-MND becomes MND-D. ALS with cognitive impairment is ALSci and with behavioral impairment ALSbi, also mentioned as ALS-FTD and with Alzheimer's like clinical pattern ALS-D. Originally called Pick's disease, the cases without Pick bodies became FLD, then FTD then FTLD, then again frontal and temporal variant of FTD, behavioral variant (FTD-bv) and semantic dementia and so on, seemingly a never-ending process of labeling and relabeling. Unfortunately, attempts to standardize terminology have not been successful, although consensus conferences are numerous. The FTD meeting four years ago in London, Ontario, summarized the democratic vote of the participants for each term in usage, but there seems to be no appetite for discipline in following them. This is most unfortunate and hinders the recognition of the understanding and relationship of the clinical patterns and pathological variants, making it impossible for an outsider to follow the literature without a comprehensive glossary.

The overlap between FTD and MND is not restricted to the ubiqutin positive tau negative inclusions. It looks like tau abnormalities may be present and therefore ALS may have something in common with the rest of FTD/Pick complex, which is tau positive! Strong and Yang explore the tau abnormalities in ALS, and the extent of glial and filamentous tau seems proportional to the degree of cognitive deficit in ALS. The overlap is further evidenced by case reports of the extrapyramidal syndromes of CBD/ PSP with the MND-type inclusions. Those who accept the tau positive – tau negative dichotomy in FTD must take warnings from these finding, before splitting the clinical or the pathological entity of FTD or FTLD.

The original genetic linkage of FTD families to chromosome 17 by Wilhelmsen and coworkers included amyotrophy. Since then, several of these families had features of MND, but not the ones with tau mutation. Wilhelmsen and others have recently described a very interesting family with tau and synuclein pathology combined with motor neuron disease in several members, and linkage to another locus on chromosome 17 distal to tau, bridging several pathologies. He reviews other cases with similar combinations and other chromosomal linkages and model systems suggesting avenues for further research to find a connection between familial FTD and MND-MND. Hardy and others also provide a genetic overview and the opening of new molecular mechanisms of cell degeneration.

Clinical and pathological summaries of FTD and ALS are provided respectively by Freedman and Brockington and associates. Freedman uses clinical vignettes to highlight the behavioral symptoms and summarizes what is known about the treatment of FTD, and the ALS chapter provides the clinical, pathological and genetic summary of ALS including the mutations of SOD1 dismutase –Familial ALS story. Murphy and others provide bi-directional statistics from combined efforts of an active ALS and FTD group, estimating ALS to be 15% in FTD which is higher than most FTD groups come up with. They also have high rates for the executive and behavioral abnormalities in ALS delineating the spectrum in its full extent including evidence from neuroimaging. Appel et al add the Texas experience of the performance of a cohort on a battery of neuropsychological tests. Tanaka describes the Japanese historical case of ALS with Dementia and cerebral blood flow and metabolic studies in ALS.

A prospective cognitive and cerebral metabolic study of primary lateral sclerosis by Grace et al from London, Ontario, shows the degree of cerebral involvement in this condition, which was considered a disease of the spinal cord in the spectrum of motor neuron disease. Kipps provides a brief glimpse of the Cambridge experience. Neuroimaging abnormalities more specific to ALS, such as the hyperintensity of the corticospinal tract (seen on T2-, proton density- and FLAIR-weighted sequences) and hypointensity of the motor cortex (seen on T2-weighted sequences) have been identified and Pioro extensively reviews these. Nuclear imaging techniques, such as positron emission tomography (PET), single photon emission computed tomography (SPECT), or functional MRI, may reveal imaging abnormalities prior to brain atrophy detection by routine MRI. A dazzling array of new imaging techniques are being applied to ALS and ALS-FTD opening possibilities for research and early diagnosis. Abrahams and associates further review functional imaging, particularly linguistic and executive frontal functions and the use of disease specific isotope ligands. Cairns, Bigio and Katsuse et al, in their respective chapters provide different perspectives and insights in their review of the neuropathology and molecular biology of FTD-ALS.

Much of the information available in this volume is novel and inspiring. The chapters are focused, some are comprehensive, and many contain original or recent work and generally represent the best research internationally in an expanding field. Dr Strong and the contributors must be commended for their effort and enthusiasm. The readers will be well rewarded when they pick up the volume and researchers well served by the content. It will be an important reference for some time to come.

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Preface

It has been both clinically and biologically convenient to consider that amyotrophic lateral sclerosis (ALS) is a disease restricted to the motor system. Clinically, this conceptualization has allowed both clinicians and researchers the luxury of treating or studying a disorder in which the fundamental target system for degeneration is the motor system.

While this belief still remains at the core of ALS, the tenant that ALS is a disease process restricted to the motor system is no longer a tenable conceptualization. Nowhere is this more evident than in the recognition that a significant proportion of ALS patients will have, at some level, one or more syndromes of frontotemporal lobar dysfunction. The clinical recognition of this fact heralds an absolutely critical change in thinking regarding the biology underlying ALS. Thus, either ALS is a discrete disease entity in which frontotemporal lobar dysfunction may occur by chance alone, or ALS with dementia or frontotemporal lobar dysfunction represents the intersection of two relatively uncommon diseases with common biological origins. The former allows one to continue to focus on the development of disease modifying agents directed towards remediating the motor system deficit. The latter however mandates that the development of disease modifying therapies addresses a continuum of disease process that may or may not respond to similar interventions. In the most rudimentary terms, if the latter is true, then modifying the disease process of motor neuron degeneration in ALS may leave an equally devastating frontotemporal lobar degeneration unchecked.

The manuscripts in this text delve into the complexity of this issue, examining the process of frontotemporal lobar degeneration and dementia in the motor neuron diseases, including ALS, from a number of vantages. The initial chapters may lead the reader to believe that there continues to be little doubt that a dementia or cognitive syndrome occurs with ALS; yet, historically, ALS is held to rarely, if at all, be associated with dementia. The historical origins of this concept are reviewed, as is the evidence that ALS, regardless of geographic site of origin (e.g., western Pacific, Japanese populations), can be associated with either dementia or cognitive dysfunction. The key issue remains not whether these co-exist, but to what extent. We have addressed this in detail.

It is perhaps too easy to state that dementia or a frontotemporal lobar degeneration is a non-motor manifestation of the disease process of ALS. To understand exactly what this means, the subsequent chapters have addressed the neuroanatomic basis of the neuropsychological syndromes of ALS and the related motor system disorders. As described by several authors, dynamic neuroimaging is increasingly a critical tool in both the clinical investigator's and the biologist's armamentarium with which to interrogate the fundamental basis by which the frontal lobes are affected in ALS, and the extent to which this degeneration yields specific neuropsychological deficits. The extent to which the structural and functional pathology observed by such techniques is a reflection of cellular neuropathology is not known. Indeed, amongst the greatest challenges of this next phase of our understanding of ALS and syndromes of cognitive dysfunction will be the need to integrate the exquisite neuropathological studies of ALS with our clinical and neuroimaging advances. In this sense, there is an urgent need to harmonize terminologies between the clinical and neuropathological 'camps' studying this aspect of the motor neuron diseases. Only through rigorously constructed prospective clinicopathological studies will this be resolved.

Finally, the molecular signature of cognitive impairment in ALS is also discussed, both within the context of the spectrum of the frontotemporal dementias and in ALS with cognitive

impairment. The modern concept that the frontotemporal lobar degenerations can be defined on the basis of both neuropathological and neurochemical characterization, in addition to genotyping where indicated is critical to advancing our understanding of ALS. Applying these tools will undoubtedly lead to a greater understanding of this disorder.

This text represents an attempt to bring together leading authorities on not only ALS, but also on the frontotemporal dementias, to enhance our understanding of the neurobiology of ALS. The papers presented here reflect those presented at the First International Conference on ALS and Dementia held in London, Ontario, in May 2005. Here, for the first time, presentations from seemingly divergent areas of interest were brought together to review critical aspects of dementia in ALS. Paramount amongst the achievements from this conference was the recognition that our understanding of cognitive dysfunction and dementia in ALS is embryonic, and that the conference represented a solid foundation upon which to move forward. In a similar spirit, it is my hope that this text will serve not as the final word on this aspect of ALS, but as a solid foundation upon which clinicians, care-givers, and researchers with a focus on ALS can begin to understand this increasingly recognized aspect of the disease.

Michael J Strong

Acknowledgments

As with all endeavors of this magnitude, this book has not been created in isolation. I owe a tremendous debt of gratitude to close colleagues who helped in the formulating of the First International Conference on ALS and Dementia, including Drs. Bruijn, Freeman, Grace, Ince, Leigh, and Lomen-Hoerth. Kelly Cornish has been a patient and diligent development editor on behalf of Informa Healthcare, to whom I am grateful. The care with which color plates have been reproduced, a critical aspect of this text, has tremendously augmented its utility as a reference standard. Editing manuscripts for the better part of eight months has been a schizophrenic existence – in part exhilarating in seeing the depth of knowledge that authors have brought to bear on this topic; in part frustration in expending large parcels of time in completing the necessary tasks. The latter would have been unbearable without the unwavering support of my family, Wendy, Jennifer, James and Alec. For this, I am grateful.

Finally, to the patients, families and caregivers that have encouraged the continued pursuit of understanding the true breadth of the disease process in ALS, I am truly indebted. It is inconceivable to those not involved in treating individuals with ALS, the emotional turmoil that must be raised when one learns that not only do they suffer from a horrendous disease such as ALS, but that there must be more than meets the eye. It is yet again another marker of just how tremendous a patient population that we are privileged to treat.

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Frontotemporal dementia in ALS: lessons from history

Arthur J Hudson

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) has long been viewed as a pure motor neuron disease, but it has become increasingly clear that it is part of an extensive central nervous system disorder.[1–4] We have become aware of this clinically in the now well-recognized association of dementia and parkinsonism with ALS and the pathological changes occurring in the brain, additional to the previously familiar upper and lower motor neuron loss, as described by Marion Smith in 1960.[5] I shall deal with the dementia aspect as it is mainly frontotemporal but discuss, as well, the association of parkinsonism with ALS because of the pathological findings which they share. My focus shall be to historically bring together and make connections, first between Guamanian ALS/parkinsonism-dementia (commonly known as the ALS/PD complex) and encephalitis lethargica ALS-parkinsonism, and then compare these with classical ALS, as they were the forerunners of our becoming aware of frontotemporal dementia and parkinsonism in ALS generally. Consistent with the times, the perspective is mainly clinical and, to a significant extent, my own views to which some current more scientifically advanced observations have been added.

GUAMANIAN ALS (ALS/PD)

It may be said that Lou Gehrig brought public awareness to ALS but Guam stimulated research. The ALS/PD complex was first recognized and intensively studied on the island of Guam in the early years following World War II.[6,7] It was subsequently discovered in two other western Pacific regions, the Kii peninsula of Japan and west New Guinea. Among the indigenous Chamorro population of Guam, ALS/PD in the 1950s had a high average incidence of 50 cases per 100 000 for males and 20 per 100 000 for females and by 1980 the incidence had fallen to less than 5 per 100 000 for both males and females.[8] Clinically, Guamanian and classical ALS are remarkably alike and the parkinsonism was also similar to paralysis agitans, the familiar form of Parkinson's disease. However, unlike paralysis agitans, dementia accompanied the parkinsonism and their occurrence together was sufficiently frequent for them to be designated 'the PD complex' by Hirano and his colleagues.[6] Only about 7% of all of the total cases of ALS, parkinsonism and dementia cases on Guam showed, clinically, a combination of all three conditions. According to Hirano, only very few ALS cases showed intellectual

loss, although they had frontotemporal pathological changes identical to the exclusively (clinically non-ALS) parkinsonism-dementia cases.[6,7,9–11] The low level of clinical expression of dementia in Guamanian ALS is also characteristic of classical sporadic ALS.

The pathological changes in ALS/PD cases were neuronal loss, gliosis and neurofibrillary tangles, granulovacuolar bodies and Hirano bodies scattered throughout the nervous system but were found mainly in the frontotemporal cerebral cortex, hippocampus, substantia nigra, locus caeruleus, dentate nucleus and anterior horn cells.[6,7,12] The distribution and character of the pathological changes were similar to classical ALS except for the neurofibrillary tangles and granulovacuolar degeneration that are usually not seen in classical ALS. Although tangles are characteristically absent in classical ALS it is worth noting that these changes seem to occur only in long-standing conditions and in cases of prior cerebral infection and therefore in Guamanian ALS the tangles may have antedated the comparatively short-lived history of ALS.[10] Evidence in support of this was the presence of neurofibrillary degeneration in the brains of the unaffected Chamorro population. Hof and Perl[13] have described how the neurofibrillary pathology can vary greatly from one subject to the next and the numbers of neurofibrillary tangles in a particular region can reflect the degree to which ALS, parkinsonism or dementia are expressed. A fascinating feature of ALS on Guam is its close resemblance to postencephalitic ALS, and a brief history of the island's occupants may offer some insight into the pathogenesis of both diseases.

John Steele[14] has described the tragic existence of the Chamorros, the indigenous people of Guam, a century and a half after Ferdinand Magellan during his circumnavigation of the world, dropped anchor at Umatac on Guam in 1521. He found them, at the time, healthy, skilled in fishing, horticulture and navigation. In the seventeenth century a devastating conflict resisting Hispanic colonization reduced the population of these formerly peaceful and industrious inhabitants from 17 000 to 1600 subjects. Subsequently, traders and various other visitors brought tuberculosis, leprosy, and epidemics of smallpox and measles with the result that, by the early nineteenth century, the Chamorros had become socially and economically impoverished. In 1898, as an outcome of the Spanish American war, Guam was taken by the United States and, as before, little attention was paid to the Chamorros who continued to live a subsistence lifestyle. With the end of World War II, their condition changed as care for the people and research on ALS/PD and other diseases began, prompted in part by the appearance in 1947 of two further epidemics, Japanese B encephalitis and mumps, that affected mostly Guamanians but also other occupants of the island.[15]

Controversy surrounding the earliest observations and interpretations of the cause of ALS on Guam were intense as different groups of American investigators visited and studied the diseases. After extensive study, some investigators thought that ALS/PD was caused by the consumption of the toxic cycad seed (*Cycas circinalis*) while another group favoured a deficiency of calcium in the soil leading to aluminum uptake in place of calcium.[8,16] Those who supported calcium deficiency rejected the cycad hypothesis and, in turn, the mineral hypothesis was refuted when the calcium content in the food and soil was found to be adequate.[17] It is noteworthy, however, that Donald Mulder[18] who participated in the studies maintained that encephalitis had been endemic on the island and the parkinsonism, in his view, was postencephalitic in origin, similar to parkinsonism which he had earlier described as a sequel to western equine encephalitis in Colorado. Asao Hirano,[9] in his study of ALS/PD on Guam, noted the absence of oculogyric crises and other features that are characteristic of parkinsonism occurring as an outcome of encephalitis lethargica and was sceptical of its relationship to ALS/PD. Nevertheless, the specter of encephalitis remained because of its relationship to both ALS and parkinsonism.

POSTENCEPHALITIC ALS-PARKINSONISM

Encephalitis lethargica and its aftermath of ALS and parkinsonism were described by von Economo, who first witnessed the disease in

1915.[19] The Spanish flu appeared shortly after the appearance of the encephalitis in 1918 as a pandemic and although it coincided with encephalitis lethargica over the ensuing years there is no evidence of the two diseases being related.[20,21] Encephalitis lethargica persisted as a worldwide pandemic until about 1925, with a morbidity that is said to have been between half a million and 5 million people worldwide.[22,23] The acute and generally protracted neurological symptoms and signs were, in variable degree, agitation, hallucinations, confusion, hypersomnolence, chorea, and the ocular abnormalities of oculogyric crises, ophthalmoplegia, and iridoplegia. ALS and parkinsonism occurred as sequelae of the encephalitis and appeared during the early period of the illness or following a delay of up to 30 or more years. They occurred together, versus occurring independently, as ALS-parkinsonism in about two-thirds of the cases.[23,24]

The actual incidence of ALS and parkinsonism accompanying lethargic encephalitis is not known. Nonetheless, the association of ALS and especially the more frequent association of parkinsonism with the encephalitis is well recognized.[23] As in the case of Guamanian ALS, postencephalitic ALS is clinically identical in appearance to classical ALS but the pathological appearance is different because neurofibrillary tangles are present in the postencephalitic and not in the classical cases. Also different, frontotemporal dementia that is clearly a clinical feature of both Guamanian and classical ALS cases is not described in postencephalitic ALS, although intellectual impairment described in other ways, such as confusion and emotional instability following the encephalitis, certainly occurred. Indeed, the pathological changes, consisting of neuronal loss, neurofibrillary tangles and gliosis, have been found extensively in the cerebral cortex and subcortical nuclei in postencephalitic ALS-parkinsonism and are very similar to the changes in Guamanian ALS/PD.[25]

Because of the similarity of both the clinical and pathological changes, such as the prominence of parkinsonism and the distribution of the neurofibrillary tangles in the postencephalitic and the Guamanian cases, they appear to share a common underlying process but for this we need to examine more recent cases of encephalitis lethargica.[25] Otherwise, a relationship between classical sporadic ALS and either of these disorders remains unclear, a subject to which I shall return shortly.

RECENT ENCEPHALITIS LETHARGICA-LIKE CASES

With the decline in the numbers of the encephalitis lethargica patients in the late 1920s and the ALS and parkinsonism sequelae over the ensuing 30 years it was assumed by many that encephalitis lethargica would completely vanish. However, von Economo[19] early on dismissed this view. He cited Sydenham who described an illness called *febrilis comatosa* in London occurring from 1673 to 1675 and suggested that this was probably the same as encephalitis lethargica. He was convinced that an epidemic in northern Italy called Nona in 1890 and 1891 was also an outbreak of encephalitis lethargica. Indeed, encephalitis lethargica-like illnesses have not vanished but have continued to appear, sporadically and worldwide, to the present.[26–29]

The initial symptoms in the recent encephalitis cases were severe and influenza-like and were followed by neurological symptoms of somnolence, hyperactivity, oculogyric crises, parkinsonism and other features as described above and as recorded by von Economo during the 1915–1925 pandemic. Whereas parkinsonism is described, ALS does not appear to have been reported in recent cases, but neither had it been in many cases of encephalitis lethargica during the pandemic. But ALS can occur as a sequel to infection and I will describe such a case of my own. Before doing so some background of the laboratory data in the recent encephalitic cases is necessary as they have been reported and interpreted by the authors in their attempt to explain the cause of the parkinsonism and ALS in encephalitis lethargica.

In a series of 20 patients with an encephalitis lethargica-like illness reported by Dale and his colleagues,[29] the authors found an elevated protein and oligoclonal banding in the cerebrospinal fluid (CSF). Others have also made this observation.[28,30] In all, 95% of their patients had

autoantibodies reactive against human basal ganglia antigens and an autopsy in one case showed striatal encephalitis and perivenous B- and T-lymphocyte infiltration. In addition, 65% of the patients had an elevated anti-streptolysin-O titer. The latter finding raised the possibility of an associated streptococcal infection producing a post-streptococcal autoimmune disease that affects the basal ganglia and other parts of the nervous system in encephalitis lethargica similar to what is seen in Sydenham's chorea following rheumatic fever.[31] Sydenham's chorea usually appears several months after the streptococcal infection and all other manifestations of rheumatic fever have abated. In support of the encephalitis lethargica-like syndrome, including the appearance of parkinsonism, being secondary to certain autoantibodies directed against gray matter neurons, two recent cases have responded favorably to treatment with methyl prednisolone.[32] However, there have been other patients who have not responded to steroid treatment and it remains unclear whether post-encephalitic ALS and parkinsonism are caused by anti-neuron antibodies.

An elevation of protein and/or oligoclonal bands in the CSF and inflammatory changes in the nervous system have been well described features in both the original and other recent cases of ALS and parkinsonism in encephalitis lethargica. In 1928 Wimmer and Neel[33] described protein increase in the CSF and perivascular cuffing of lymphocytes and inflammatory nodules in the spinal cord in cases of encephalitis lethargica with ALS. In a well illustrated recent case of encephalitis lethargica-like syndrome with parkinsonism, Kiley and Esiri[28] also showed oligoclonal bands in the CSF and perivascular infiltrates of plasma cells that were distended with IgG in the brainstem and diencephalon. The perivascular infiltrates in the midbrain and basal ganglia were identified as both T and B cells.

ALS FOLLOWING SEVERE LOCAL INFECTION

A patient whom I attended did not have encephalitis but developed ALS following a massive local suppurative lesion due to a cat bite to the dorsum of the right foot.[34] Within 6 months of the bite, and after the lesion had healed, she developed left foot drop followed by weakness of the left leg. Weakness and wasting spread to involve both legs and over the succeeding months advanced steadily upward to the cervical region, culminating in death from pulmonary failure a year from onset. On laboratory examination, there was oligoclonal banding in the CSF.

At autopsy ALS was confirmed and sections of the spinal cord and medulla also showed perivascular cuffing by lymphocytes (notably plasma cells) and inflammatory nodules that consisted of clusters of astrocytes, microglia and an inflammatory core in the pontomedullary junction. Both the CSF and autopsy findings were unusual for classical ALS and resembled those reported in both the original and recent encephalitis lethargica cases. No viral inclusions or viral or bacterial antigens have been identified in our patient, lethargica-like cases or any of the archival brains of encephalitis lethargica or postencephalitic parkinsonism cases.[20,21,28,29]

Parkinsonism has occasionally been associated, as an early and late sequel, with a number of other epidemic viral encephalitides such as Japanese B encephalitis, St Louis encephalitis, Western equine encephalitis and Australian X disease but, unlike encephalitis lethargica, no mention appears to have been made of ALS.[18,35] If ALS is a very late sequel of infection its association may not be recognized. Based on antibody studies, some investigators have contended that in some cases of parkinsonism the prior encephalitic infection had been occult and the infecting virus had persisted and become active in the brain even decades later, a phenomenon well recognized in the invariably fatal disease subacute sclerosing panencephalitis (SSPE) occurring as a late sequel to the measles virus.[35,36] However, the brain cells in SSPE do show serological and electron microscopic evidence of measles virus infection. It is the recovery of the infectious virus that is difficult, requiring co-cultivation of the brain tissue with indicator cells.[37]

CLASSICAL SPORADIC AND FAMILIAL ALS

The importance of the discussion so far has been presented as a means toward understanding

classical sporadic and familial ALS. Since ALS became a disease of the upper and lower motor neurons in the classical descriptions of Charcot[38] in 1869 and others in the nineteenth century occasional reports of patients have appeared describing ALS as being accompanied by dementia, psychosis, parkinsonism, aphasia, and various other neurological disorders.[39]

In 1960 Marion Smith[5] showed that classical sporadic ALS cases, with clinically none other than muscle wasting and upper motor neuron signs, had more extensive pathological changes in the nervous system than the well-recognized anterior horn cell loss and pyramidal tract degeneration. These changes were typically present in the frontotemporal cortex and many subcortical nuclei – notably the thalamus, corpus striatum, globus pallidus, subthalamic nuclei, and substantia nigra. Similar changes have been observed in familial ALS, both cortical and subcortical and, in addition, degenerative changes in the spinal cord. Thus, from autopsy findings, both classical sporadic and familial ALS had varying degrees of extensive although mild, and not clinically apparent, neurodegenerative changes.

Classical ALS with frontotemporal dementia and parkinsonism

In classical sporadic and familial ALS, frontotemporal dementia is much more commonly associated with ALS than is parkinsonism, in contrast to the Guamanian ALS in which parkinsonism with dementia is more prominent.

In the sporadic cases of *ALS with dementia and/or parkinsonism* the degenerative changes in the cortex and subcortical nuclei are much more striking than in ALS without clinical signs of dementia.[23] Autopsies on familial cases are fewer than the sporadic cases but the pathological findings are similar. The cortical involvement in both is predominantly frontotemporal and consists of a spongiform appearance, gliosis and loss of neurons in layers 1, 2, 3, and less frequently layers 5 and 6. In its minimal state only the first layer of the cortex appears to be affected and has a spongy appearance. While the findings in ALS with dementia are predominantly frontotemporal in location the pathological changes in the cerebral cortex can be more extensive involving, for example, the insular and cingulate cortices. Degenerative changes in the subcortical nuclei in ALS-dementia are variable and also quite extensive. These include the basal ganglia, thalamus, hypothalamus, hippocampus, subthalamic nucleus, substantia nigra, red nucleus, periaqueductal gray, locus caeruleus, and olivary nuclei, and the changes are usually much more striking and wider in distribution than those in cases of ALS without dementia, especially in the clinically more seriously affected cases. Of interest, involvement of the basal ganglia and substantia nigra in ALS with dementia without reported clinical evidence of parkinsonism is frequent. The pathological findings in sporadic ALS cases with *both* dementia and parkinsonism are very similar to patients with ALS and only dementia.

The relationship between sporadic and familial ALS

Skepticism has often arisen about the relationship of familial ALS and parkinsonism to sporadic ALS. However, as discussed above, families with either or both dementia and parkinsonism have remarkably similar clinical and pathological features to the sporadic disease.[23] Some pathological differences in familial cases in comparison with the sporadic disease have been described, such as a higher incidence of posterior column degeneration and a predisposition to degeneration of Clarke's column and spinocerebellar tracts. However, this does not disqualify a relationship to the sporadic disease. The main cause of familial ALS can be ascribed to mutations in the Cu/Zn superoxide dismutase (SOD1) gene, but its role in the disease appears to be a gain of function in which the mutant SOD1 protein accumulates in the cell, with the most deleterious effects occurring within the mitochondria.[40] The absence of SOD1 or other evidence of an inheritable disease in sporadic ALS does not preclude a genetic etiology with a similar pathogenesis.

DISCUSSION AND CONCLUSION

The historical interpretation reached with the three different forms of ALS – Guamanian

ALS/PD, postencephalitic ALS-parkinsonism, and classical sporadic and familial ALS – is how fundamentally alike they are. All these forms of ALS are accompanied to different degrees by frontotemporal dementia and parkinsonism and show widespread distribution of the degenerative changes in the frontotemporal cerebral cortex and subcortical nuclei. However, frontotemporal dementia is a much more prominent feature than the parkinsonism in sporadic and familial ALS, whereas parkinsonism, with or without dementia, is the more prominent characteristic in the Guamanian and postencephalitic diseases. On the basis of neuropathological studies, Guamanian and postencephalitic forms most resemble one another in the presence of neurofibrillary tangles that are not found in sporadic ALS. It is recognized that postencephalitic ALS and parkinsonism are the sequelae to infection of the nervous system and Guamanian ALS/PD, believed by many to be related to environmental factors, might also be related to a prior infective illness. The sporadic form of ALS with its associated frontotemporal dementia and parkinsonism may have a different etiology and, in kinship with familial ALS, may have a similar pathogenetic basis. In all types of ALS, environmental factors such as infection may be coupled as a precipitative effect on a particular genetic or immune vulnerability.[41,42]

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2

Frontotemporal dementia – current concepts

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HISTORICAL CONTEXT

Interconnected nomenclatures have developed based on clinical, pathologic and genetic criteria for a collection of syndromes related to what is now called frontotemporal dementia (FTD). Clinicians, pathologists and geneticists have developed these nomenclatures to reflect organizing principles useful to their disciplines that were cognizant of contemporary developments in other disciplines. Further insight into the etiology and pathogenesis of these disorders is needed before these nomenclatures can coalesce. The lack of one to one correspondence between these nomenclatures makes it inappropriate to use them interchangeably (see Table 2.1).[1] Historically, clinical and pathologic heterogeneity, as well as the features that led to the lack of one to one correspondence between nomenclatures, led to the proliferation of eponyms and a perception that these conditions could not be identified correctly in life that pervaded most of the twentieth century. Advancements in clinical assessment, neuroimaging, molecular techniques and molecular genetics led to the 'rediscovery' of these conditions and the proliferation of eponyms.

The first reports of FTD were made by Arnold Pick between 1892 and 1906.[2,3] Pick described disturbances in judgment, asocial behavior and aphasia with focal frontal and temporal brain atrophy at post mortem without further histological evaluation. In recognition of Pick's insight, Kertesz has suggested that a series of named conditions with frontal and temporal atrophy within the clinical spectrum described by Pick be called 'Pick complex'.[3] The first histological evaluation of brains with focal frontal and temporal brain atrophy detected argyrophilic globular inclusions that are now called Pick bodies. For many investigators, Pick bodies became pathognomonic for what is now eponymously referred to as Pick's disease. Most cases with the syndrome described by Pick do not have Pick bodies.[1,4]

Systematic pathologic examination of brains from autopsy series of demented patients without Alzheimer's disease or patients who had differences in cerebral blood flow from patients with Alzheimer's disease led to several groups elaborating on the clinical syndrome described by Pick and its associated pathology.[5–10] A key advancement for the field was the specification for clinical and pathologic diagnostic criteria for FTD.[11,12] Many researchers have recognized that patients with FTD could have a positive family history and that many individuals are affected in some families.[13–15]

Table 2.1 Varying nomenclature of FTD and related syndromes

Clinical nomenclature	*Genetic nomenclature*	*Pathologic nomenclature*
FTD	FTDP-17	Tau inclusion
Frontal variant	with tau mutations	3R
Orbitobasal	without tau mutations	4R
Medial	Tau associated	3R and 4R
Dorsolateral with motor neuron disease	FTD linked to chromosome 3	Tau inclusion-negative ubiquitin inclusion-positive
Temporal variant	FTD and ALS	Dementia lacking distinguishing histology
Semantic dementia	Chromosome 9 linked	Frontal variant of AD
Nonfluent aphasia	Chromosome 17 linked	Other
PSP	FTD with Pagets	
CBD	FTD with myotonic dystrophy	
Frontal variants of Alzheimer's	Sporadic	
Dementia with parkinsonism	Other	
Amyotrophy with dementia		
Other		

During the same time period that the Lund and Manchester groups were laying the foundation for the FTD nomenclature, my laboratory used genetic analysis to map the mutation for the most common familial form of FTD to chromosome 17q21-22.[15] This analysis was done by defining a clinical syndrome called disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC) that is inherited in family Mo. A literature review at the time revealed that DDPAC was clinically related to the condition described in many families (see Lynch et al.[16] and online associated supplementary tables). Patients with DDPAC met the then new diagnostic criteria for FTD.[17] Subsequently, disease was shown to segregate with 17q21-22 for a series of families with named syndromes.[18] As a group these cases are referred to as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17).[19]

Most cases of FTDP-17 are due to mutations in the microtubule-associated protein tau gene (*MAPT*).[20–23] FTDP-17 cases with *MAPT* mutations all have aggregated tau protein in neurons or glia. Tau has been the subject of intense study because it is the major constituent of the neurofibrillary tangles that are a key pathologic finding in Alzheimer's disease.[24] Alzheimer's disease and FTDP-17 are members of a large group of disorders with aggregated tau, including some that overlap clinically and pathologically with FTD, that are collectively referred to as tauopathies.[25–27] The biology of tau is now being extensively characterized. It appears that tau plays a central role in the Alzheimer's-FTD spectrum[28,29] and may have a critical role in the pathogenesis of many other tauopathies. Recently, a consensus pathology diagnostic scheme has been proposed for FTD and several related disorders that depends on the biochemical analysis of tau.[1]

Although the progress that has been made in characterizing and understanding the pathogenesis of FTD has been satisfying there is still a need for additional progress. It is critical that clinical, pathologic, and genetic nomenclatures eventually converge and that we develop an understanding of how FTD is related to other disorders. Progress will be made by further clinical, pathologic and biochemical characterization of these disorders as well as the identification of new genetic factors that affect susceptibility and progression. This review will begin with a description of the function and role

of tau in FTD because it is so central to our current understanding of the FTD pathogenesis and then summarize what is known about FTD and related disorders from the perspective of pathologists and clinicians. An emphasis has been made to describe the most recent contributions to the literature and cite recent reviews for older literature.[29–41]

MICROTUBULE-ASSOCIATED PROTEIN TAU AND FTDP-17

Tau genomics and biochemistry

The function and biology of tau have been extensively described in the literature.[29,37,38,40,42] *MAPT* is located on chromosome 17q21-22. There are homologous genes located elsewhere in the genome. These genes appear to compensate for the loss of tau in mice in which the gene has been deleted. Tau 'knockout' mice appear to be essentially normal.[43] *MAPT* is located within a several million base pair region that is resistant to meiotic recombination (unpublished observation). About 35% of Europeans have at least one chromosome 17 where there is an inverted 900 000 base pair segment of DNA which contains *MAPT*. Individuals with this inversion have what is called the H2 haplotype.[44] Only the alternative haplotype, H1, is found in populations from Africa or Asia. Meiotic recombination in individuals with the H1/H2 genotype could lead to dicentric chromosomes which are unstable. It is likely that selection pressure resulted in the higher frequency of the H2 in Europeans. Stefansson et al. observed that the H2 haplotype carriers have more children and higher rates of genome wide recombination.[44] Whether these observations are related to tau function is uncertain.

The *MAPT* is distributed over 120 000 base pairs of DNA that include several large introns (UCSC Genome browser, http://genome.ucsc.edu). The *MAPT* has 15 exons that are translated or partially translated with a complex pattern of differential splicing.[45] Exons 4A and 6 have been detected in mature transcripts in the peripheral nervous system. Exon 8 has not been detected in mature transcripts in humans although it is normally transcribed and translated in other mammals. In the central nervous system six tau isoforms are produced by differential splicing of exons 2, 3, and 10. The mature transcripts that include exon 10 code for a protein that has four microtubule binding domains (4R). Translation of transcripts without exon 10 leads to protein with three microtubule binding domains (3R). Exon 10 has large flanking introns that contain complicated repetitive sequences which may have a role in splicing regulation. Approximately half of CNS transcripts contain exon 10. Independent of exon 10 splicing, transcripts are commonly observed that contain both exons 2 and 3 (2N), just exon 2 (1N), or neither exons 2 or 3 (0N).

The functional protein products of the *MAPT* gene are thought to have little secondary structure when they bind tubulin and promote its polymerization into and stabilize microtubule formation. Microtubules and tau play critical roles in intracellular transport of organelles. Microtubules are continuously assembled and disassembled in a dynamic process that is modulated in part by tau function. Tau function is modulated by phosphorylation and dephosphorylation of more than 25 different amino acids. In general phosphorylation reduces the binding of tau to microtubules. The regulation of tau phosphorylation by kinases and phosphatases and the degree with which tau modulates interaction of other molecules is an area of active investigation. One of the most extensively investigated tau kinases is glycogen synthase kinase-3β, which in turn is involved in a complex regulatory cascade.[46]

The regulation of the differential splicing of exon 10 has the potential to dramatically affect microtubule formation and presumably stability as 4R tau increases the *in vitro* rates of microtubule assembly 2.5–3.0 times relative to 3R tau. In addition 4R tau *in vitro* and *in vivo* has a greater ability to assemble into filaments that are presumed to have pathologic significance.[47] The effect of differential splicing of exons 2 and 3 on tau function is less certain.

The clinical spectrum of FTDP-17

Linkage analysis in rare, very large kindreds, established that a locus for familial dementia segregated with chromosome 17q21-22.[15,18] Most

of the families initially linked to 17q21-22 had previously been described in the literature with unique names and clinical descriptions including: disinhibition-dementia-parkinsonism-amyotrophy complex,[16] pallido-ponto-nigral degeneration,[48,49] hereditary dysphasic dementia,[50] familial progressive subcortical gliosis,[51,52] and familial multiple system tauopathy.[53] Most families described after the publication of the Lund and Manchester consensus for FTD and in whom linkage analysis to 17q21-22 has been established, have been described as having familial FTD.[54,55] A consensus conference held in Ann Arbor, Michigan suggested the name FTDP-17 to describe linked families.[19]

More than 40 *MAPT* mutations in more than 100 families have been reported in the literature.[29,38,40,42,56] Although *MAPT* mutations are often described synonymously with FTDP-17, there are several families with convincing linkage to 17q21-22 in which systematic attempts to find mutations in *MAPT* have failed. Most efforts to find mutations have focused on exons and flanking intronic sequences. It is still possible that sequences that affect tau biology play a role in the FTDP-17 families in which tau mutations cannot be found.

The clinical spectrum associated with *MAPT* mutations extends beyond the latest consensus diagnostic criteria for FTD.[12] It should not be inferred that the current consensus criteria should be changed, but strongly suggests that the current criteria will need to be updated in the future. *MAPT* sequence should only be used to help guide further developments in nosology since most patients with FTD do not have *MAPT* mutations. There is substantial clinical and pathologic heterogeneity between patients with the same mutations even within the same families.[16,57,58] This clinical and pathologic heterogeneity among cases with a common etiology should encourage inclusion of related clinical syndromes.

All the clinical subtypes described in the current consensus criteria for FTD have been shown to be caused by mutations in *MAPT*. Some mutations are reported that have more prominent amyotrophy.[16,59] Other mutations are associated with clinical features that resemble progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).[39,60] A Spanish kindred has been described where subjects homozygous for an amino acid deletion have atypical PSP and carriers have probable Parkinson's disease. Patients with pallido-ponto-nigral degeneration typically also have prominent parkinsonism and many have retrocollis.[49] Another *MAPT* missense mutation has been associated with FTD with prominent parkinsonism and seizures.[61]

The pathologic spectrum of FTDP-17

All *MAPT* mutations that cause the spectrum of disease related to FTD have aggregated hyperphosphorylated tau in neurons and/or glial cells in either cortex, subcortex or spinal cord.[62,63] The biochemical and morphologic properties of aggregates and the type of cells that contain aggregates tend to be the same for patients with the same mutation.[37] Some patients with FTDP-17 that are *MAPT* mutation-negative have ubiquitin-positive, tau-negative inclusions.[63] This supports the conclusion that FTDP-17 is actually two distinct conditions.

The pathologically defined syndromes associated with tau mutation in addition to FTD pathology (including Pick's disease) described by Arne Brun[64] include: PSP, CBD, argyrophilic grain disease,[36,39] and neurofibrillary tangle only disease.[20,65] Specific tau mutations have been reported to have a predilection for these syndromes and FTD with motor neuron disease.[39] There are reports of the same mutation causing different pathologic syndromes in different families.

MAPT mutations

The more than 40 known tau mutations affect tau biology by changing a single amino acid or by affecting the differential splicing of exon 10 to change the relative amount of 3R vs 4R tau (for recent reviews, see Dermaut et al.,[29] Rademakers et al.[37] and Goedert[39]). Some mutations in exon 10 have the potential to affect both splicing of exon 10 and the primary amino acid sequence of tau. Most of the tau mutations missense mutations are in the carboxy end of the protein, in or near the microtubule binding

domains. Two missense mutations have been identified in exon 1.[66,67] Most of the *MAPT* mutations that change the amino acid sequences also reduce the ability of the tau protein to interact with microtubules and increase its propensity to assemble into abnormal filaments.[39,68,69]

Nearly half the FTDP-17 patients have mutations that have the potential to affect the regulation of exon 10 splicing, disrupting the ratio of 3R to 4R isoforms.[39,69,70] Mutations that affect the differential splicing of exon 10 include both missense and synonymous mutation in the coding sequence and mutations in the sequence 3′ to exon 10. Both mutations in exon 10 and 3′ intronic sequences have the potential to disrupt putative splicing regulatory sequences, including a sequence that is dyad-symmetric that spans the intron–exon junction.[71–73] Messenger RNA transcripts of dyad-symmetric sequences have the theoretical potential of forming a 'hair-pin' structure that could affect transcript maturation.

Amino acid changes that are coded for by exon 10 can only be found in 4R isoforms. It should not be surprising that aggregated hyperphosphorylated tau found in FTDP-17 patients with exon 10 mutations might only contain 4R tau. Since 4R tau has a greater tendency to aggregate *in vitro*, as described above, it should not be surprising that some mutations that are not coded for by exon 10 are also associated with aggregates that only have 4R tau. What is surprising is that the hyperphosphorylated tau aggregates found with some mutations only contain 3R tau. This is surprising since mutant 3R and 4R as well as normal 3R and 4R tau are made in the brains of these individuals and all isoforms are included in the hyperphosphorylated tau aggregates for Alzheimer's disease.[37] It is possible that allelic exclusion or imprinting is used such that only one chromosome is used to make tau in each cell. Cell type-specific regulation of splicing is also possible, as suggested by the data of Nishiura and colleagues.[74] They observed that even though all six tau isoforms are found in hyperphosphorylated aggregates in Alzheimer's disease, glial tau aggregates do not appear to have peptides coded for by the differentially spliced exon 3.

The large number of mutations that have been identified and the pace with which new mutations are continuing to be identified suggest that for the foreseeable future DNA resequencing will be the strategy of choice for screening patients for *MAPT* mutations. There are a few mutations that are more common than others, particularly in certain geographic regions. There is evidence that a common ancestor is responsible for a *MAPT* mutation found in several families,[75] but most mutations appear to be sporadic.

MAPT genetics in other tauopathies

Typically, the direct DNA sequence comparison of any two chromosomes will detect a difference within every thousand base pairs. Many of these sequence variants will be essentially unique to an individual and their relatives. Other sequence variants will be present in a significant fraction of the population. Both types of changes have the potential to affect an individual's susceptibility to disease. The effect of the common variants can be measured by assessing the risk for developing disease among people that have a variant (or genotype) and those that do not. Analysis of the common DNA sequence variants for the tau gene has revealed that knowing which common variant is found on a chromosome often allows one to predict which of the variants will be present for most of the other polymorphisms. The information about which variants are present on a chromosome is called a haplotype. The tau gene has two common haplotypes called H1 and H2.

Most individuals that have PSP and CBD are homozygotes for the H1 haplotype.[36,39,76,77] It is uncertain whether being homozygous for the H1 haplotype increases risk or whether having a copy of the H2 haplotype decreases risk. It should be reinforced that most of the population is homozygous for the H1 haplotype. Tau haplotype data are of little utility for establishing the diagnosis of CBD or PSP.

The relationship between *MAPT* haplotypes and susceptibility to FTD and FTDP-17 is less certain. We have found that *MAPT* haplotypes tend to be associated with FTD (unpublished observation), whereas others have found no association.[78] Borroni et al. found an association

between *MAPT* haplotype and age of onset of FTD.[77] It is possible that the effects of *MAPT* haplotype on FTD susceptibility are entangled with the effects of other genotypes such as *APOE*. If there is any effect of *MAPT* haplotype on FTD susceptibility it is small. Definitive proof that *MAPT* haplotype affects FTD susceptibility will require large patient samples with systematic collection of relevant clinical data (e.g. age of onset).

Martin et al.[79] (reviewed by Spillantini and Goedert[80]) have reported that one of the strongest linkage signals detected for familial idiopathic Parkinson's disease (IPD) has been on chromosome 17 near the *MAPT* locus and that they observed an association between familial IPD and polymorphisms in the *MAPT* locus. This observation requires additional replication before the results can be considered proven.

MAPT in model systems

Genetic manipulation of *MAPT* in cells and organisms has been used to study the biology of tau and to create model systems to investigate the pathogenetic consequences of *MAPT* mutations.[40] The systems studied have their strengths and limitations, such that their relevance to FTDP-17 is uncertain. Transgenic expression of human tau with mutations that cause FTDP-17 in *Caenorhabditis elegans* resulted in a more severe neurodegenerative phenotype than wild-type tau.[81] Overexpression of the human *MAPT* homologue in *Drosophila melanogaster* in neurons induced apoptotic neuronal cell death without aggregated tau protein.[82] Transgenic expression of *MAPT* with amino acid substitutions that cause FTDP-17 results in mice that have aggregated hyperphosphorylated tau, with behavioral and neurodegenerative changes that fall within the spectrum of disease observed in FTDP-17.[83–85]

Genetic models of tauopathies provide the opportunity to perform detailed biochemical, cellular and system analysis that is not possible in humans. The models that have been developed, although not perfect, can be used to screen pharmacologic interventions for effectiveness. At a minimum these systems will improve our knowledge of the pathogenesis of FTD and related disorders.

Non-*MAPT* genetics of FTD

In addition to FTDP-17 without *MAPT* mutations, there appears to be another locus on chromosome 17, distal to *MAPT*, which causes FTD and ALS with tau and α-synuclein containing inclusions.[86] We have sequenced the exons for more than 20 genes in the support interval without detecting mutations that are likely to be causal (unpublished results). Yancopoulou et al. have reported a family with familial progressive aphasia who developed features of frontotemporal dementia with predominant tau pathology but also α-synuclein pathology.[87] They were unable to find tau or synuclein mutations and have not mapped the locus responsible by linkage analysis.

Hosler et al. have used linkage analysis to several families ascertained through individuals that present with ALS and dementia to chromosome 9q21-22.[88] The dementia in these individuals apparently meets clinical criteria for FTD. The mutation responsible for this condition has not been identified.

One of the first large kindreds identified with FTD is genetically distinct from FTDP-17.[89–91] Affected members of this Danish kindred meet the Lund Manchester criteria for FTD but have more diffuse pathology that results in global reduction in cerebral blood flow as measured by PET scanning. There are limited tau inclusions in neurons and glial cells.[92] Linkage analysis mapped the trait to chromosome 3 and mutations in CHMP2B subunit of the endosomal ESCRTIII complex were identified.[93] The same group identified a second mutation in CHMP2 in an independent case of FTD but concluded that mutations in CHMP2 do not appear to be a common cause of FTD. CHMP2B was originally identified in a yeast mutagenesis screen for dysmorphic hybrid vacuole-endosome organelles. It is assumed that the protein also plays a role in endosomal function in mammalian cells.

Two syndromic causes of familial FTD have also been identified. Le Ber reported a single family with myotonic dystrophy and histologic

pattern of neuronal loss and spongiosis seen in FTD with tau inclusions with probable linkage to 15q21-24.[94] Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia (IBMPFD) has been shown to be linked to 9p13-p12.[94] Six mutations have been detected for this syndrome in a valosin-containing protein (*VCP*).[95] *VCP* has been associated with many essential cellular functions. It is particularly interesting that the protein product of *VCP* is aggregated IBMPFD and that *VCP* expression can modulate the impact of polyglutamine expansions in model systems.

FTD PATHOLOGY

Constantinidis et al. divided their cases with the clinical syndrome described by Pick with focal frontal and temporal atrophy into group A, with Pick bodies and swollen acromatic neurons (called Pick cells); group B, with Pick cells only; and group C, with only gliosis but neither Pick cells or bodies.[4] This classification system is quite adequate to describe most of the cases that Pick described clinically and effectively encompasses pathologies described by the Lund and Manchester groups[96] for FTD and by Knopman et al. for dementia lacking distinguishing histology.[5] The approach taken by Brun[64] from the Lund group focused more on the topology of cell loss than Constantinidis and the current focus on special stains, biochemistry, and cell morphology. The enthusiasm for the use of special stains and biochemical methods is in part due to the assumption that these methods provide insight into the pathogenesis of these disorders. These analyses can more directly interrogate the state of proteins known to participate in the pathogenesis of disease.

A recent consensus conference on the clinical and pathologic diagnosis of FTD recommended an algorithm where tau and ubiquitin immunohistochemical staining and biochemical assessment are a routine part of the pathologic evaluation.[1] Cases are stratified into those with only tau inclusion, only ubiquitin inclusions and neither tau nor ubiquitin inclusions. Cases with tau inclusions with neuronal loss and gliosis are further divided based on the number of microtubule-binding domains present in the hyperphosphorylated aggregated tau. 3R tau only is a characteristic of the disease with Pick bodies and FTDP-17. 4R tau only is a characteristic of FTDP-17, PSP and CBD. Disease with hyperphosphorylated aggregated 3R and 4R is associated with FTDP-17 and neurofibrillary tangle only disease (and Alzheimer's disease). Cases with ubiquitin inclusions, neuronal loss and gliosis are associated with FTDP-17 without tau mutations and FTD with motor neuron disease. Neuronal loss and gliosis in the absence of tau and ubiquitin inclusions is associated with what Brun called frontotemporal lobar degeneration and Knopman et al. called dementia lacking distinguishing histology.

The difficulty in quantifying subcortical neuronal loss contributes to the limited description of subcortical involvement in FTD. The dopaminergic cells of substantia nigra are an exception because the nigra is identifiable during gross dissection and dopaminergic cells have distinctive morphology with standard histology. Literature exists for a pathologically defined syndrome called progressive subcortical gliosis that clinically overlaps with FTD and can be due to mutations in *MAPT* in which subcortical gliosis was particularly striking.[51,52] It is likely that all the subtypes described in the consensus of McKhann et al.[1] can have minimal or prominent loss of nigral dopaminergic cells and that parkinsonism can result from a variety of subcortical pathologies.[97]

Motor neuron involvement is frequently observed in post-mortem examination of FTD and FTDP-17. FTD with motor neuron disease has tau inclusions if tau mutations are present and ubiquitin inclusions if tau mutations are not present.[98]

PSP and CBD are distinguished from FTD with tau aggregates by the distribution of degeneration and cell morphology.[99] In general CBD has more cortical involvement, while PSP has greater brainstem involvement. CBD is associated with severe neuronal depletion, swollen achromatic neurons, and diffusely staining tau-positive astrocytic plaques in the cortex, with prominent subcortical changes in the basal ganglia.[100,101] PSP is characterized by neurofibrillary tangles and/or neuropil threads, particularly in the basal ganglia, brainstem,

cerebellum, and prefrontal cortex. In PSP, tau aggregates in the astrocytic processes and bodies leading to the formation of a tufted astrocyte.[36]

The relative percentage of the pathologies observed in FTD varies between groups.[102] The FTD with Pick's bodies varies from 8% to 35%. There is consensus that frontotemporal lobar degeneration (also known as dementia lacking distinguishing features) and FTD with ubiquitin-positive inclusions are the two most common pathologic causes of FTD. The fraction of cases that have tau aggregates varies depending on whether CBD and PSP cases are ascertained. The rate of tau mutations also varies from <1% to 14%.[102] In our experience the rate of mutation in patients with fewer than two first-degree relatives with FTD is about 1%.

CLINICAL AND NEUROIMAGING DEFINED FTD AND RELATED SYNDROMES

The clinical phenomenology of FTD has recently been extensively reviewed.[1,30,31,103] FTD occurs primarily between the ages of 35 and 75 with a mean age of onset of 53 in one study.[104] There are reports of very early age of onset[105] and that mutation carriers have early neuropsychological changes.[106] Incidence data for FTD are very limited, in part because most cases of FTD also meet criteria for Alzheimer's disease[107] and most epidemiologic studies have not detected FTD reliably even though current criteria for FTD are reasonably sensitive and specific.[108] The prevalence of early-onset (<65 years) FTD and Alzheimer's disease are approximately the same with a prevalence of 15 per 100 000.[102,104] Forty-five percent of patients with FTD are reported to have a positive history for FTD or other neurobehavioral disorder.[109] Patients typically have a rapidly progressive course with a median survival of 9 years from onset of symptoms.[110,111] The prognosis is worse if there is motor neuron disease.

The descriptions by Pick indicate that he appreciated that the clinical presentation of patients with focal frontal and temporal atrophy is variable. Patients with FTD typically present with changes in behavior or language. Within these groups additional distinctions have been made. At the end of life patients with FTD become more homogeneous. The observed variability on presentation can be explained by brain systems affected. While this is usually reflected in the location of the initial focus of atrophy, it is not reflective of the type of microscopic pathology. As the name FTD implies, involvement of both frontal and temporal lobes is common, with variable involvement of subcortical structures and motor neurons. Neuroimaging and clinical assessment led to the recognition that some patients present with predominantly frontal or temporal lobe involvement (known as frontal and temporal variants of *FTD*; fvFTD and tvFTD). Patients with FTD, fvFTD and tvFTD can have either predominantly right or left hemispheric degeneration. PSP and CBD have historically been considered as movement disorders. These syndromes are increasingly recognized as cognitive disorders that overlap with FTD.[36,97,99,100,112,113] PSP is characterized by relative preservation of cognitive function with prominent postural instability and eventually gaze palsy. CBD is characterized by a progressive, asymmetric, akinetic, rigid syndrome, with prominent apraxia, myoclonus, cortical sensory loss, cognitive impairment, and rarely alien limb behavior.

Frontal lobe dysfunction can result in different syndromes depending on which systems are disrupted first.[31] Patients who present with orbitobasal dysfunction have disinhibition, poor impulse control, antisocial behavior, and ritualized behavior. Patients with medial degeneration present with apathy, while patients with dorsolateral dysfunction have trouble with planning and organization. Patients with these syndromes can also have motor neuron disease or extrapyramidal dysfunction. Patients that present with the tvFTD have behavioral problems if the right side is more affected and problems with language if the left side is more affected. Gorno-Tempini et al. have clinically divided patients with language difficulties into semantic dementia with anterior temporal lobe atrophy, nonfluent progressive aphasia with left inferior frontal and insular atrophy, and logopenic progressive aphasia with posterior temporal cortex and inferior parietal lobule atrophy.[114] Semantic dementia is characterized by fluent speech with loss of semantic

knowledge. Patients with nonfluent progressive aphasia have apraxia of speech. Logopenic progressive aphasia is characterized by slow speech output.

CONCLUSION

Progress in clinical, pathological and genetic understanding of frontotemporal dementia in the last two decades has been substantial. A syndrome that is one of the most important causes of presenile dementia has gone from being routinely misdiagnosed to being widely recognized. Mutations in the *MAPT* gene are now recognized as an important cause of familial FTD and related disorders. Model systems have been developed for the disease and are being used to test new therapies.

The clinical and pathologic phenomenology needs further elaboration so that there is a better correspondence between clinical and pathological diagnosis. The remaining genetic contribution to FTD needs to be elucidated. We would like to know why patients with the same mutations present with different clinical and pathological syndromes. Model systems offer the opportunity to understand the pathogenesis of FTD and the etiologic relationship with other disorders. The observation of allelic association between tau polymorphisms and familial Parkinson's disease[115] and that mutations in Presenilin 1 (the most frequent cause of familial Alzheimer's disease) can cause FTD including disease with Pick bodies without amyloid plaques[116–119] are intriguing. These observations suggest that the cellular processes in these common neurodegenerative diseases may overlap and that progress in any of these diseases may lead to progress in all of them.

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3

Clinical phenomenology and treatment of frontotemporal dementia

Morris Freedman

INTRODUCTION

Frontotemporal dementia (FTD) is a common cause of dementia under age 70 years,[1–3] and occurs in 8–17% of cases with dementia in this age group based upon neuropathological series.[4,5] FTD is part of a spectrum of disorders encompassed by the broader entity of frontotemporal lobar degeneration (FTLD) that includes progressive nonfluent aphasia and semantic dementia.[6] FTD is a behavioral syndrome whereas progressive nonfluent aphasia and semantic dementia are syndromes related to deficits in language and semantic knowledge, respectively. FTD, progressive nonfluent aphasia, and semantic dementia share the same spectrum of pathologies but differ clinically due to different lesion sites.[6] The focus of this chapter is to review the neurobehavioral features of FTD, as well as the emerging literature on treatment of FTD. There will also be a brief overview of progressive nonfluent aphasia and semantic dementia.

TERMINOLOGY AND DIAGNOSTIC CRITERIA

The literature on FTLD contains a variety of different terms that have been used to describe the same syndromes.[7] For example, whereas Neary et al. applied the term FTLD to the overarching disorder and FTD to the behavioral presentation,[6] others have used FTD as the broad label and frontal variant FTD (fvFTD) for the behavioral syndrome.[8] Other examples of differences in terminology are temporal lobe variant FTD[9,10] and progressive fluent aphasia[8] for semantic dementia. In addition, primary progressive aphasia has been used to encompass both progressive nonfluent aphasia and semantic dementia.[11] Moreover, Pick complex has been proposed as a term that encompasses all of the preceding syndromes plus corticobasal degeneration, progressive supranuclear palsy and FTD with motor neuron disease. The term Pick complex highlights the clinical and neuropathological overlap among these syndromes.[11,12]

In 1994, the Lund Manchester criteria for FTD were published.[13] Although they were widely used, these criteria essentially comprised a checklist without guidelines defining the number of features required for diagnosis. In 1998, Neary et al. reported a consensus statement which provided an update and extension of the earlier Lund Manchester criteria.[6] Another set of diagnostic criteria was published in 2001 by the Workgroup on Frontotemporal Dementia and Pick's Disease.[14] These criteria use the term FTD to encompass the behavioral syndrome and

the language presentation. In addition, the language presentation includes both progressive aphasia and semantic dementia.

The Neary criteria provide well-defined and detailed descriptions of each of the three syndromes comprising FTLD and are thus well suited for subject selection in research trials. Knopman et al.[15] examined the accuracy of ante-mortem diagnosis of FTLD against neuropathological diagnoses. Their series consisted of 34 cases with pathological FTLD among 433 consecutive patients who underwent autopsy. Ante-mortem diagnosis of FTLD was based on the sum of clinical, neuropsychological and imaging features derived from the criteria presented by Neary et al.[6] The sensitivity was 85% with a specificity of 99%. The approach taken in this chapter will be to use the terminology and classification system proposed by Neary and colleagues, i.e. FTLD as the overarching disorder with FTD, progressive non-fluent aphasia and semantic dementia as the syndromes encompassed by FTLD.[6]

CLINICAL FEATURES

FTD

Based on the Neary criteria (Table 3.1), there are five core diagnostic features required for a diagnosis of FTD. In addition to insidious onset and gradual progression for at least 6 months, these consist of the following early features: loss of insight, decline in social interpersonal conduct, emotional blunting, and impaired regulation of personal conduct.[6]

Loss of insight occurs early in the illness in the setting of relatively well-preserved cognition in areas outside the social cognitive realm. The following is a case example:

> *Case DL:* A high functioning woman developed a significant change in behavior that included a decline in social cognitive function. She was diagnosed with FTD and was informed of this diagnosis by her neurologist. Although DL retained the knowledge that she had been given a diagnosis of FTD, i.e. she recalled being told that she had FTD, she was insistent that she had no problems and that she was fully capable of working. To assess her insight and awareness, her neurologist asked her to participate in role play where she pretended to be an employer who had to make a decision about hiring a man who had been diagnosed with FTD. As was the case with DL, the man felt that he did not have any cognitive or behavioral problems. Thus the

Table 3.1 The clinical diagnostic features of FTD: clinical profile

I. Core diagnostic features
- A. Insidious onset and gradual progression
- B. Early decline in social interpersonal conduct
- C. Early impairment in regulation of personal conduct
- D. Early emotional blunting
- E. Early loss of insight

II. Supportive diagnostic features

- A. Behavioral disorder
  1. Decline in personal hygiene and grooming
  2. Mental rigidity and inflexibility
  3. Distractibility and impersistence
  4. Hyperorality and dietary changes
  5. Perseverative and stereotyped behavior
  6. Utilization behavior
- B. Speech and language
  1. Altered speech output
     - a. Aspontaneity and economy of speech
     - b. Press of speech
  2. Stereotypy of speech
  3. Echolalia
  4. Perseveration
  5. Mutism
- C. Physical signs
  1. Primitive reflexes
  2. Incontinence
  3. Akinesia, rigidity, and tremor
  4. Low and labile blood pressure
- D. Investigations
  1. Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder
  2. Electroencephalography: normal on conventional EEG despite clinically evident dementia
  3. Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality

role play involved DL having to make a decision about hiring someone who was essentially in the same situation as she was in. DL enquired whether she would have access to information that the applicant had FTD and was advised that she would be given this information. The examiner then asked DL whether she would hire the applicant. She responded 'no' and explained that she would not hire him because he had FTD and indicated that this disorder could affect his ability to work. At the end of the role play, DL was asked to 'be herself' again. The examiner then asked whether she was able to work. She replied 'Well yes I am'.

This case example indicates a marked lack of DL's insight and awareness of her deficits in relation to herself at an early point in her illness. In contrast, there is strikingly preserved awareness of the impact of FTD when applied to someone else. This illustrates that she had sufficient knowledge and understanding of FTD to know that this disorder can affect a person's ability to work. Thus DL's belief that she is capable of working is a true lack of insight into her own deficits as opposed to a lack of knowledge about the effects of FTD.

Decline in social interpersonal conduct refers to breaches of social etiquette that represent a change from previous behavior. Examples include a decline in manners and social graces, disinhibition, violation of interpersonal space, and antisocial behavior.[6] The following are case examples of a decline in social interpersonal conduct in patients with FTD:

Case RJ: A man in his 50s showed a change in behavior that initially manifested with stealing two toy airplanes from a gift shop. He subsequently continued to take other people's possessions. Other problems included poor hygiene. He also took a shower while wearing his pajamas. In addition, he started to eat food from garbage cans. When asked about this latter activity, RJ noted that he was discriminating about the food that he took from the garbage. He said that he ate the 'good' food. He was aware that others thought it 'highly abnormal' that he was eating food from garbage cans and that 'it looked bad'. However, he felt that there was nothing wrong with what he did.

Case SM: A previously shy woman started to approach strangers on the street and tried to give them hugs and kisses. After being admitted to hospital for assessment, she approached other patients and staff in the same way.

Case LT: A woman who had developed inappropriate behavior was asked to write a sentence during a mental status exam. She wrote 'I love you' to the examiner by drawing a picture of an eye, a heart, and a ewe.

Emotional blunting refers to emotional shallowness with unconcern, loss of emotional warmth, indifference to others, and a loss of empathy and sympathy.[6] Empathy refers to an awareness of the feelings of others, whereas sympathy refers to sharing these feelings. The following description by the wife of a patient with FTD (Case HR) illustrates an example of emotional blunting. In response to the examiner's question about her husband's emotions she replied: 'The changes in how he behaves are that he has become quite emotionally detached . . . He is still quite happy to see people. He will give me a hug and everything else but there is no real feeling attached anymore.'.

Impaired regulation of personal conduct refers to changes spanning the spectrum of inactivity, passivity, inertia, pacing, wandering, increased talking and laughing, sexuality, singing, and aggression.[6]

In addition to the core diagnostic features required for a diagnosis of FTD, patients may show features such as stereotypic behavior, utilization behavior, and hyperorality. Stereotypic behavior includes repetitive activities such as clapping and singing, as well as routines such as repeatedly walking along fixed routes. Utilization behavior refers to the unrestrained exploration of objects in the environment by grasping and using them.[16] Hyperorality includes overeating, food fads, and oral exploration of objects. The following excerpts from a conversation between Case HR, referred to above, and his wife illustrate features of hyperorality:

Wife: What have you taken to doing in terms of going into other people's rooms?
Case HR: Nothing.

Wife: Oh come on, what have you been doing?
Case HR: No nothing.
Wife: Remember that day when I came in and found an empty box of cookies in your room?
Case HR: Yah.
Wife: Where did you get that?
Case HR: I don't know.
Wife: Oh yes you do. What's the name of the man's room where you took it?
Case HR: No. I don't know. I just took it.
Wife: That's right.
Examiner: So you did take the cookies?
Wife: And ate them all.
Case HR: And ate them all.

Other abnormal behaviors include mental rigidity and inflexibility, distractibility and impersistence, and a decline in hygiene and grooming. Although the consensus criteria published by Neary et al. list early severe amnesia as an exclusion,[6] Hodges et al.[17] found that amnesia may be the dominant presenting symptom in a study of pathologically proven cases with FTD. In contrast, visuospatial and perceptual symptoms were absent in their series. This is in keeping with spatial disorientation as an exclusion feature in the Neary criteria.

Neuropsychological assessment

The early behavioral changes in FTD may be due to lesions in orbitomedial frontal systems.[18] This concept is supported by neuropathological data showing early involvement of orbital cortex in FTD. Broe et al.[19] staged severity of atrophy in patients with FTD who were selected from a neuropathological series of cases with dementia. They grouped the FTD cases into four stages of severity. Stage 1 represented the earliest changes and was characterized by atrophy in the orbital and superior medial frontal cortex and hippocampus. The concept that orbital pathology underlies the initial clinical manifestations of FTD suggests that standard neuropsychological tests are likely to be ineffective for detecting early FTD. The vast majority of these neuropsychological measures are sensitive primarily to dorsolateral frontal function and do not adequately assess orbitofrontal cortical function.[18,20] For assessment of early FTD, this suggests a need for the development of clinical neuropsychological measures that are sensitive to orbitofrontal system deficits.

The object alternation task, a measure of working memory for objects and ability to shift sets, is an example of an experimental test that is sensitive to orbitofrontal damage[21] and that may be adaptable for clinical use. The object alternation task is sensitive to ventrolateral-orbitofrontal (inferior frontal convexity and orbital surface) lesions in nonhuman primates[22–25] and has been validated as being sensitive to ventrolateral-orbitofrontal and medial frontal lesions in humans.[21] The neuroanatomical regions involved include Brodmann areas 10, 24, 32, and 47, and possibly 11. The object alternation task is one of the few neuropsychological tests of orbitofrontal function in humans. Freedman et al.[26] administered this task to patients with FTD and found significant impairment in this group. The sensitivity to differentiating FTD from controls was 93% at a cut-off of 23 errors. Specificity was 51%.

Tests of social cognition, such as measures of Theory of Mind (ToM), may also prove useful in the assessment of patients with FTD. ToM refers to the awareness of other people's minds and the ability to make inferences about the mental states of others.[27–30] An example of a ToM test is the first order false belief task.[31,32] A typical false belief task involves a scenario where two people are in a room (person A and B). Person A puts an object somewhere while person B watches. Person B then leaves the room. After person B leaves, person A moves the object. Person B then returns. The false belief question to the subject is 'Where does person B think that the object is?'. To answer correctly, the subject must take the perspective of person B who has a false belief of where the object is. Other ToM tasks include recognition of faux pas,[33,34] detection of deception,[30] and the Reading the Mind in the Eyes Test.[35,36]

ToM has been studied in patients with focal brain lesions and FTD. Stone et al.[33] found that patients with bilateral orbitofrontal lesions showed deficits in the ability to recognize a faux pas. Stuss et al.[30] found that patients with medial frontal lesions, particularly right ventral, were impaired on detection of deception. These

studies suggest a role for orbital and medial frontal systems in the mechanisms underlying ToM and suggest that tests of ToM may be useful in defining deficits in FTD. In support of this concept, Gregory et al.[36] studied ToM in patients with FTD and found significant deficits as measured by performance in false belief tasks, detection of faux pas, and the Reading the Mind in the Eyes Test.

Progressive nonfluent aphasia and semantic dementia

Progressive nonfluent aphasia is associated with asymmetric atrophy, affecting primarily the left frontotemporal lobes, whereas semantic dementia is associated with bilateral atrophy that is most marked in the anterior temporal lobes, with the middle and inferior temporal neocortex predominantly affected.[6] The atrophy in semantic dementia is commonly asymmetric.[37] Diagnostic criteria for progressive nonfluent aphasia and semantic dementia have been published by Neary et al.[6] Features of progressive nonfluent aphasia include insidious onset and gradual progression, nonfluent spontaneous speech, agrammatism, phonemic paraphasias, anomia, stuttering speech, poor repetition, alexia and agraphia. There is early preservation of word meaning. Behavioral characteristics of FTD may emerge as the disease progresses.

Semantic dementia is characterized by loss of meaning for words and impaired recognition of faces and objects. An example of loss of word meaning is illustrated by the following excerpts from an interview with a patient who has semantic dementia:

Examiner: Point to the watch.
Case BW: Point to my watch? I forget what is the watch, what is the watch?
Examiner: Point to the ceiling.
Case BW: Point to the ceiling, what is the ceiling? Is the ceiling here?
Examiner: There is a ceiling here, could you point to the ceiling?
Case BW: No, I don't know.

Other features of semantic dementia include insidious onset and gradual progression, fluent, empty spontaneous speech, semantic paraphasias, preserved ability to match or reproduce simple line drawings, and preserved single word repetition. Patients are able to read and write to dictation orthographically regular words, i.e. words with direct sound-to-letter correspondence, but are commonly impaired with orthographically irregular words, i.e. words that do not have direct sound-to-letter correspondence. Examples are reading 'mild' to rhyme with 'build' and writing 'flight' as 'flite'. This deficit in reading is called surface dyslexia and the writing deficit is referred to as surface dysgraphia. Features of FTD may emerge as the illness progresses.[38]

TREATMENT

Although several drugs have been tested in FTD, only four have been studied in double-blind placebo-controlled trials: idazoxan,[39] trazodone,[40] paroxetine,[41] and galantamine.[42] Significant benefit has been reported with idazoxan and trazodone in FTD. In contrast, a decline in performance was found with paroxetine. Galantamine produced benefit in primary progressive aphasia.

Idazoxan is an alpha-2 adrenoreceptor antagonist. Alpha-2 receptors act as presynaptic autoreceptors to inhibit noradrenaline (norepinephrine) release. Blockade may therefore increase noradrenaline. Idazoxan was tested using a single case cross-over design. There was improvement in tests of frontal lobe function, i.e. Tower of London, verbal fluency for category and sustained attention.[39] Trazodone was studied using a cross-over design in doses of 150–300 mg daily. There was significant benefit on the NPI total score with improvement in eating disorders, agitation, irritability, and depression/dysphoria. Thirty-one subjects were initially treated and 26 subjects completed the trial.[40] In the paroxetine trial, a cross-over design was used. Assessments were carried out at a dose of 40 mg daily. There were 12 subjects initially. Two withdrew before being tested on the drug. There are complete data for 6 of the remaining 10 subjects. The results showed a significant decline in performance on reversal learning and delayed pattern recognition, as

well as decline on paired associate learning that neared significance.[41]

Galantamine was studied in FTD and primary progressive aphasia at a dose of 16 or 24 mg per day. Patients were treated for 18 weeks and then entered a 4-week double-blind placebo-controlled withdrawal phase. Thirty-six subjects completed the open-label phase and 34 completed the double-blind phase. A significant benefit was found in patients with primary progressive aphasia in the placebo-controlled withdrawal phase on the Clinical Global Impressions. In addition, the Aphasia Quotient of the Western Aphasia Battery remained stable in the active treatment group, whereas the placebo group showed a decline.[42]

In addition to the above double-blind placebo-controlled trials, several other studies have been carried out in FTD. The drugs tested include lithium plus fluoxetine,[43] lithium plus paroxetine,[43] SSRIs (selective serotonin reuptake inhibitors),[44–47] l-deprenyl,[48] moclobemide,[49] methylphenidate,[50] piracetam,[47] donepezil,[51] and rivastigmine.[51,52] There was benefit in all cases except piracetam. Although improvement has been reported for SSRIs,[44–47] including paroxetine,[45,47] the double-blind placebo-controlled trial of paroxetine showed a decline in function on this medication.[41]

In addition to treatment of FTD with medication, there is an important role for nonpharmacological interventions.[53–55] These typically include environmental, behavioral and psychosocial strategies.[53] Research is needed to demonstrate the efficacy of these approaches in FTD in well-designed clinical trials.

CONCLUSIONS

FTD is being increasingly recognized as a common cause of dementia, particularly in patients under 70 years of age. Although there are well-defined criteria for FTD, and its related disorders that are encompassed by FTLD, progressive nonfluent aphasia and semantic dementia, there is a need for consensus on uniform terminology that can be applied across research studies and clinically. In addition, improved cognitive assessment tools are required to aid in early diagnosis of FTD. This includes the development of clinical neuropsychological measures that are sensitive to orbitofrontal lesions that may underlie the initial clinical manifestations of FTD. Also, with the emergence of pharmacologic treatment studies for FTD, there is an important need to develop consensus on standards for therapeutic trials. These include standards for diagnostic criteria, severity measures, outcome measures, and experimental design.[56] Finally, the relation between FTD and disorders such as motor neuron disease,[57–59] corticobasal degeneration,[60] and progressive supranuclear palsy[60] needs to be further defined.

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4

The clinical and pathological spectrum of ALS

Alice Brockington, Paul Ince and Pamela J Shaw

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), first described by Charcot in the nineteenth century,[1] is one of a group of diseases in which the primary disorder is of the motor neuron. The term motor neuron disease (MND), which is more commonly used in the UK, also encompasses three conditions that are considered variants of ALS: primary lateral sclerosis (PLS), primary muscular atrophy (PMA), and progressive bulbar palsy (PBP).

ALS is a neurodegenerative disorder that causes progressive injury and cell death of lower motor neurons of the brainstem and spinal cord and upper motor neurons of the cerebral cortex. It is the third most common adult-onset neurodegenerative disease, with an incidence of about 2 per 100 000. The etiology of neurodegeneration in ALS is heterogeneous: approximately 10% of cases are familial, and 20% of these are caused by mutations in the free radical scavenging enzyme Cu/Zn superoxide dismutase (SOD1). Other genetic mutations have been identified in small numbers of patients,[2–7] but in the majority of familial disease, and in patients with sporadic ALS, the cause of selective degeneration of motor neurons has not been established with certainty. A number of pathogenic mechanisms are thought to be involved in the degenerative process, including oxidative stress, excitotoxicity, inflammation, mitochondrial and neurofilament dysfunction, and ultimately activation of a programmed cell death pathway.[8,9]

ALS has traditionally been considered a pure motor disorder, but the evidence that multisystem degeneration occurs is now overwhelming. This concept is supported by occasional case studies which describe severe degeneration of other neurological systems in association with ALS, and by studies of larger series of ALS patients in which a picture of predominant motor dysfunction is accompanied by more subtle abnormalities in other systems such as sensation or cognition. The description of ubiquitinated intraneuronal inclusions in 1988 implicated a common molecular pathology in ALS. This has provided molecular pathological evidence of widespread involvement of extramotor regions of the central nervous system (CNS). Furthermore, the ubiquitinated inclusion is described in a number of related disorders, including PLS, PMA, and frontotemporal dementia (FTD), supporting the hypothesis that these conditions represent a clinico-pathological spectrum of disease.

THE CLINICAL AND PATHOLOGICAL SPECTRUM OF MOTOR DISORDERS IN ALS

Clinical features

ALS is characterized and defined by the presence of abnormalities of upper motor neurons of the cerebral cortex, and lower motor neurons of the brainstem and spinal cord.

Signs of lower motor neuron dysfunction

Lower motor neuron (LMN) degeneration causes weakness, atrophy and fasciculations of the limbs (amyotrophy, see Fig. 4.1). Muscle cramps are a common symptom, and patients may be aware of fasciculations as twitching of the muscles. In bulbar palsy, the tongue is wasted and flaccid, and speech is slurred (Fig. 4.2).

Signs of upper motor neuron dysfunction

The involvement of upper motor neurons (UMNs) is indicated by the incongruous presence of active or brisk tendon jerks in a wasted limb, the presence of the Hoffman or Babinski sign, spasticity and clonus. In pseudobulbar palsy, the snout and jaw reflexes may be exaggerated, and muscle spasticity may cause slow repetitive movements of the tongue or high-pitched, strangulated speech. Emotional lability, with difficulty controlling episodes of

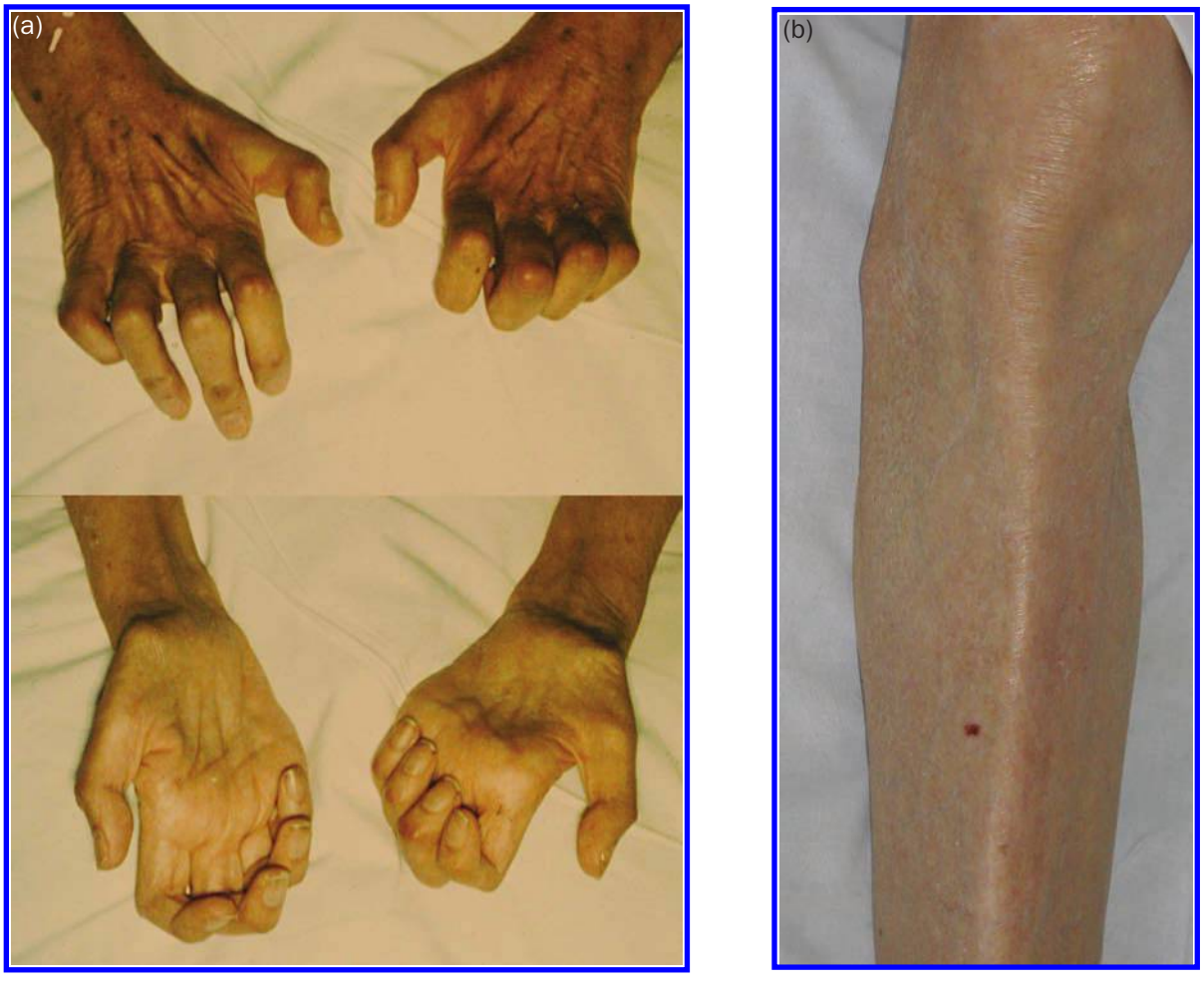

Fig. 4.1 Amyotrophy of the (a) upper and (b) lower limbs.

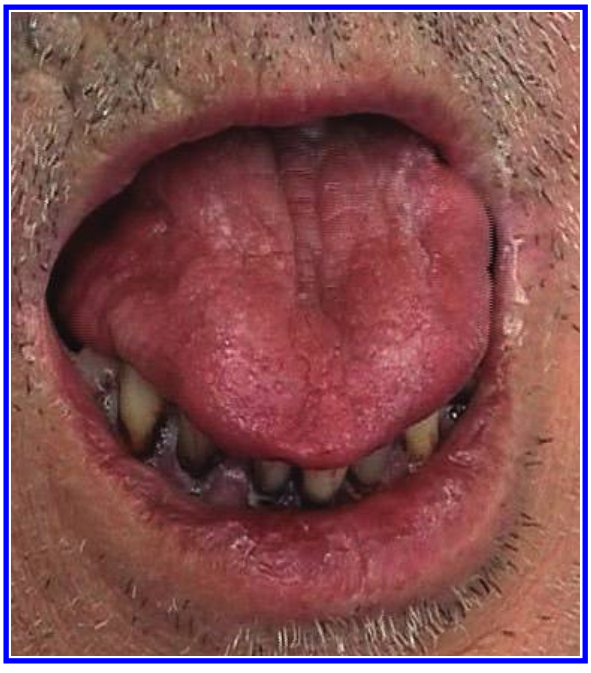

Fig. 4.2 Atrophy of the tongue in a patient with ALS.

laughing or crying, often accompanies UMN signs in the bulbar regions.

Upper and lower limb features

Symptoms begin in the limbs in 75% of patients. Asymmetry or unilaterality of symptoms and signs is common. Affected individuals may notice weakness or clumsiness of the hands, or difficulty raising the arms above the head. In the lower limbs, foot drop is a common presentation. The gait may become slowed or clumsy due to weakness and spasticity of the legs.

Bulbar features

With involvement of the bulbar region, patients complain of difficulty with speech and swallowing. Mealtimes may become prolonged and arduous, with frequent episodes of choking. Certain foods, particularly those with mixed textures, become difficult to swallow, and aspiration of food with consequent pneumonia is a constant risk. Speech becomes slurred or high-pitched and strangulated, and as the disease progresses, patients may have to use communication aids. The onset of ALS in the bulbar regions has a less favorable prognosis than limb-onset disease.

Other clinical features

Weight loss is a common feature of ALS. This is multifactorial, with loss of muscle bulk due to amyotrophy, and difficulty maintaining nutrition in the face of dysphagia, while appetite may also be affected by reactive anxiety and depression or by immobility. Severe weight loss and nutritional deficiencies may compound muscle weakness. The involvement of neck musculature is common later in the course of disease, causing difficulty holding the head upright (Fig. 4.3). Occasionally, onset of the disease in respiratory musculature causes breathlessness as a presenting symptom. Usually, respiratory failure develops insidiously during the course of the disease, causing dyspnea and orthopnea. Symptoms of nocturnal carbon dioxide retention may develop, including morning headaches, anorexia and daytime somnolence (Fig. 4.4).

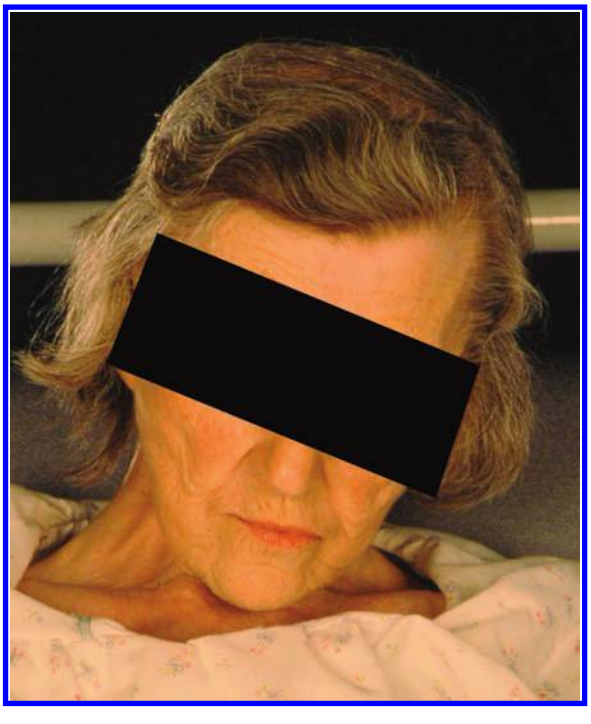

Fig. 4.3 A patient with weakness of neck extension causing dropping of the head.

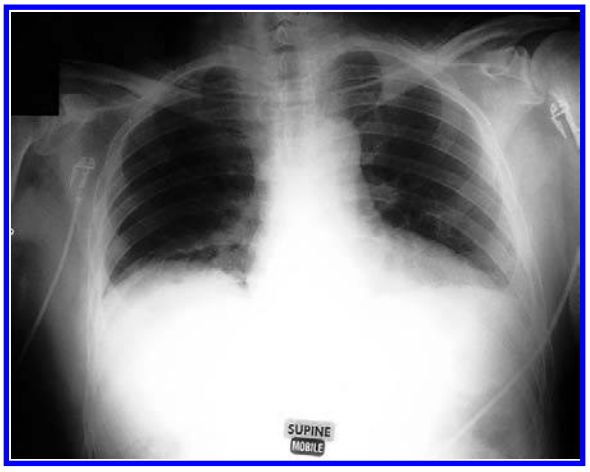

Fig. 4.4 Chest radiograph, showing elevation of the hemidiaphragms and reduced lung volumes in a patient with ALS.

Selective sparing of specific motor neuron groups

The eye movements are spared in ALS. Even in advanced disease, when patients would otherwise be 'locked in', communication can often be maintained by movements of the eyes. Similarly, the external sphincters are not typically involved in the disease process, so that patients remain continent of urine and feces.

Disease course, prognosis and death

Symptoms are often focal at onset, but there is usually evidence of more widespread motor neuron degeneration on examination, with clinical signs such as hyperreflexia or fasciculations, and on electrophysiological testing. As the disease progresses, weakness typically becomes more generalized, involving the limbs and bulbar and respiratory muscles. Mobility and upper limb function decline, and patients may become quadriplegic and entirely dependent on nursing care. Bulbar dysfunction may progress to anarthria, and enteral feeding may be required due to severe dysphagia. The mean survival from onset of symptoms is 3 years, although rapid variants of disease may progress over the course of a few months, and in some cases prolonged survival over one or two decades is described. The usual cause of death is progressive respiratory failure, or bronchopneumonia.

Epidemiology

Recent epidemiological studies provide an approximate rate of incidence of sporadic ALS of 2 per 100 000, and a prevalence of 6 per 100 000. This rate is geographically fairly constant, although pockets of high incidence are described in the Western Pacific. Among the Chamorro indigenous population of Guam, on the Kii peninsula of Japan and among the Auyu and Jakai people of Irian Jaya, ALS is found at a rate 50–100 times higher than that in US and European populations, often in association with another fatal neurodegenerative condition, parkinsonism-dementia complex. Men are more commonly affected than women in most series, with a ratio of about 1.5:1. In population-based studies, the mean age of onset is approximately 65 years, and the mean disease duration is 3 years.[10]

Segmental variants of ALS

Several variants of ALS have been described, in which the disease follows a more focal course than that described above. The flail arm syndrome (progressive amyotrophic diplegia) may occur in up to 10% of ALS patients.[11–15] It is characterized by profound symmetrical weakness and wasting of the upper limbs with hyporeflexia, that predominantly involves the proximal muscle groups (Fig. 4.5). Although signs of corticospinal tract involvement may be seen in the legs, there is little or no functional impairment of the bulbar muscles or legs at presentation, and these regions are usually involved only late in the course of the disease. It is more common in men than women, and has a longer median survival than classical ALS, of 57 months (compared with 39 months for classical ALS) in one case series.[13] A similar focal presentation in the lower limbs is recognized, although less well characterized than flail arm syndrome.

Monomelic amyotrophy (MMA) has been chiefly reported in Asia, including Japan and India, with very few cases reported from the West. This is a benign variant of motor neuron

Fig. 4.5 The flail arm segmental variant of ALS.

disease that predominantly affects young men, aged about 20 years. Wasting and weakness are usually confined to one upper or lower limb, without involvement of cranial nerves, pyramidal tracts, sensory, cerebellar, extrapyramidal or cortical functions. Some patients develop similar symptoms in the contralateral limb, but symmetrical involvement is very rare. In the vast majority, the onset is insidious, with a slow progression over 2–4 years, followed by a stationary phase.[16,17] It does not evolve to ALS.[18] A neurogenic pattern on electromyography, and histologic evidence of neurogenic atrophy suggest an underlying anterior horn cell lesion. Benign MMA was first described in the distal upper limb in young Japanese men by Hirayama in 1959.[19] This variant of MMA is referred to as Hirayama's syndrome. Two autopsies of patients with Hirayama's syndrome showed anteroposterior flattening of the spinal cord at C7 and C8 with necrosis of the anterior horns. This finding, and the observation that there is forward displacement of the dural canal during neck flexion in patients with Hirayama's syndrome, has led to the proposal that displacement of the dural canal and compression of the spinal cord may underlie the condition.[20]

Primary lateral sclerosis

Primary lateral sclerosis (PLS) is a disorder of spinobulbar spasticity, with sclerosis of the lateral tracts of the spinal cord, first described by Erb in 1875.[21] It is a sporadic disorder with insidious onset, and usually starts in the fifth decade or later as a spastic paraparesis. Bulbar or upper limb onset also occurs. The course is gradually progressive, and although patients ultimately develop a severe spastic spinobulbar paresis, survival is usually prolonged compared with patients with classical ALS.[22]

The differential diagnosis of this symptom complex is wide, and includes hereditary spastic paraparesis, multiple sclerosis (MS), neurosyphilis, human T-cell leukemia virus (HTLV-1) associated tropical spastic paraparesis, human immunodeficiency virus (HIV) myelopathy, spondylotic myelopathy, and compressive lesions of the foramen magnum. Not all case series described have adequately excluded these

alternative diagnoses, particularly prior to the availability of modern imaging techniques, serological tests for syphilis and viral infections, and vitamin B12 assays. This has led to debate in the past as to the existence of PLS as a distinct disease entity.[22] The controversy was addressed in 1992, by Pringle et al., who described a case series of eight patients with progressive symmetric spinobulbar spasticity in whom the above diagnoses were excluded, and proposed diagnostic criteria for PLS[22] (Table 4.1).

Although the clinical picture of PLS is dominated by UMN involvement, in most case series described, there is evidence clinically or electrophysiologically of mild changes of denervation indicating degeneration of lower motor neurons, which may only develop after several years.[22–25] The evolution of PLS into ALS has been described, with the onset of generalized amyotrophy developing after many years of a slowly progressive spinobulbar spasticity,[26] and PLS may occur as a phenotypic manifestation of familial ALS.[27] These findings raise the probability that PLS is part of the spectrum of ALS, with predominant but not exclusive degeneration of upper motor neurons.

Progressive muscular atrophy

This phenotype denotes a pure LMN degeneration, in the absence of UMN signs. Patients presenting with pure LMN signs will often evolve into classical ALS, acquiring brisk reflexes and upgoing plantars at a later stage of disease. In those that maintain a pure LMN phenotype, the differential diagnoses of X-linked spinobulbar muscular atrophy (Kennedy's disease), adult forms of spinal muscular atrophy (SMA) caused by SMN gene mutation, and multifocal motor neuropathy with conduction block must be considered. As with PLS, there has been debate as to whether patients with PMA represent part of the spectrum of ALS. Clinical methods to detect UMN involvement may be unreliable late in the disease, when there is severe global weakness and amyotrophy.

Progressive bulbar palsy

Onset of ALS in the bulbar regions is most common in women of middle to elderly age, and usually progresses to involve the limbs. Some patients with bulbar onset will not develop limb

Table 4.1 Diagnostic criteria for PLS[22]

Type of criteria	*Features*
Clinical criteria	Insidious onset of spastic paraparesis, usually beginning in lower extremities, but occasionally bulbar or in the upper extremities Adult onset, usually fifth decade or later Absence of family history Gradually progressive course Duration ⩾ 3 years Clinical findings limited to those associated with corticospinal dysfunction Symmetrical distribution, ultimately developing severe spastic spinobulbar paresis
Laboratory criteria (exclusion of alternative diagnoses)	Normal serum chemistry, including vitamin B12 levels Negative serological tests for syphilis (and Lyme disease and HTLV-1 in endemic areas) Normal CSF parameters with absence of oligoclonal bands Absent denervation potentials on EMG or at most, occasional fibrillation and increased insertional activity in a few muscles (late or minor) Absence of compressive lesions of cervical spine or foramen magnum (spinal MRI scanning) Absence of high signal lesions on MRI similar to those seen in MS

CSF, cerebrospinal fluid; EMG, electromyogram; HTLV-1, human T-cell leukemia virus-1; MRI, magnetic resonance imaging; MS, multiple sclerosis. (Reproduced from[22] by permission of Oxford University Press.)

weakness in the course of their illness, although clinical signs of UMN or LMN dysfunction may be present in the limbs on examination. This variant is known as progressive bulbar palsy (PBP).

Pathological features of ALS

Gross pathological changes

The gross pathological changes of ALS comprise atrophy of the cerebral precentral gyrus, and shrinkage, sclerosis and pallor of the anterolateral tracts of the spinal cord (Fig. 4.6). There is thinning of the hypoglossal nerves and anterior spinal roots, and somatic musculature is atrophied.

Lower motor neurone pathology in ALS

ALS patients will typically have lost 50% of their anterior horn cells in the spinal limb enlargements at autopsy, although there is considerable variation between patients and between different spinal levels.[28] Many of the remaining lower motor neurons show atrophic and basophilic changes that may represent part of the spectrum of a programmed cell death pathway.[29] This neuronal loss is associated with diffuse astrocytic gliosis. There is relative sparing of the motor nucleus of Onufrowitz (Onuf's nucleus) in the S2 spinal segment,[30] which innervates skeletal muscles of the pelvic floor to control bladder and bowel function, and the cranial motor nuclei of the oculomotor, trochlear and abducens nerves. These findings correlate with retention of urinary and fecal continence, and the preservation of eye movements in ALS. Although inclusion bodies, such as ubiquitinated inclusions, are described in Onuf's nucleus in ALS patients,[31–33] implying that it is subject to the same pathological processes as other somatic motor neuron groups, neuronal numbers are maintained. The selective resistance of these two groups of motor neurons in ALS is unexplained. Hypotheses proposed include absence or paucity of direct corticospinal monosynaptic innervation, the size of neurons and differences in neurophysiological activity, and differences in levels of calcium binding protein expression compared with other motor neuron types.[34]

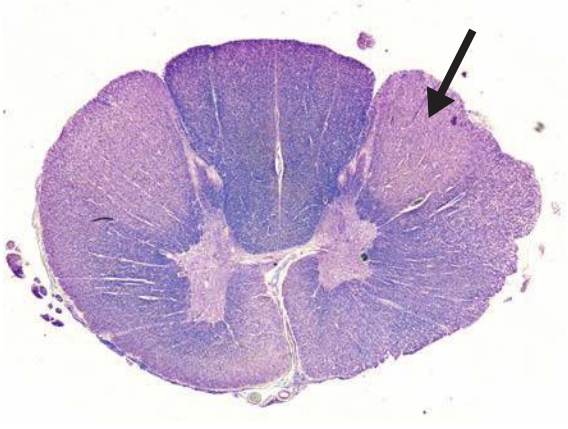

Fig. 4.6 Thoracic spinal cord showing diffuse lateral and ventral tract pallor due to myelin loss in the descending tracts (arrow, lateral corticospinal tract; Luxol Fast blue).

The key feature of lower motor neuron pathology in ALS is the presence of inclusion bodies within the soma and proximal dendrites, as described below. Note that the nomenclature of intraneuronal inclusions in ALS is varied. Publications prior to the recognition of ubiquitinated inclusion bodies refer to round inclusion bodies on conventional stains that show variable appearances, including basophilic, eosinophilic, and amphophilic with a peripheral halo resembling Lewy bodies. These have been referred to as 'Lewy-like' or 'Lewy-like hyaline inclusions'. Since the advent of ubiquitin immunochemistry in ALS, these have been shown to be ubiquitinated inclusions, which do not contain α-synuclein, and the designation 'Lewy-like' is therefore unhelpful. The term 'hyaline inclusions' has been used in the past to refer both to ubiquitinated inclusions, and to neurofilament conglomerate inclusions, which are larger, more prominent and argyrophilic.

Ubiquitinated inclusions

Ubiquitinated inclusions (UBIs), first described in 1988,[35,36] are the most frequent neuronal lesion of sporadic ALS, with a prevalence of virtually 100%.[37,38] The few cases in which they are not found include atypical cases, and those with very severe neuronal loss and atrophy at end-stage disease. Some familial cases of ALS are also

characterized by absence of UBIs, and these are discussed in more detail below. UBIs show a morphological spectrum extending from a few filamentous thread-like ubiquitinated profiles, through skeins of varying compactness, to more compact spherical bodies[39] (Fig. 4.7).

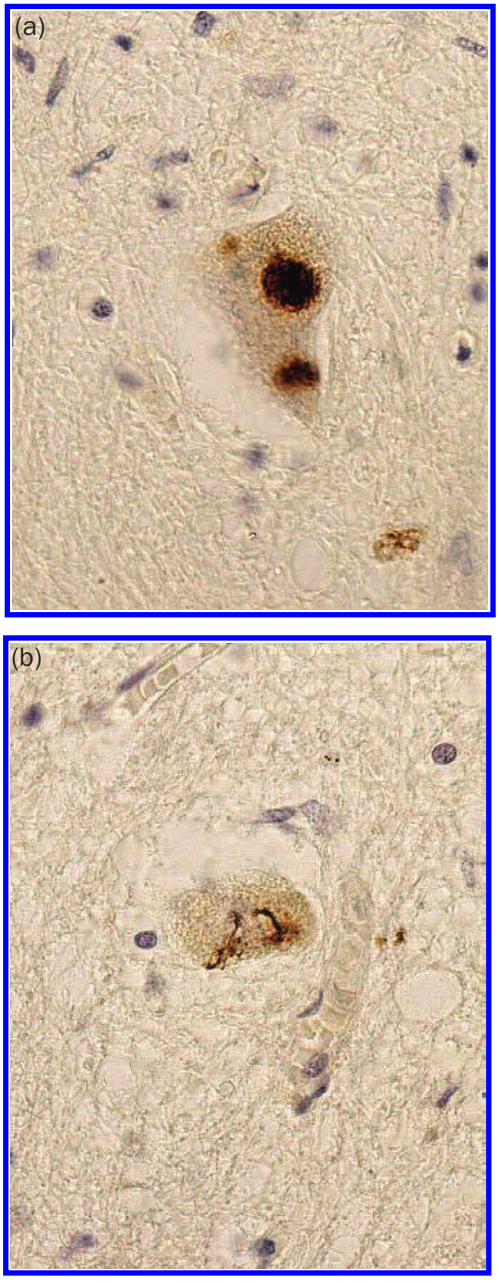

Fig. 4.7 Ubiquitinated intraneuronal inclusions in spinal lower motor neurons showing compact (a) and skein (b) morphology (ICC for ubiquitin).

Ubiquitin is a small highly conserved protein which becomes covalently bound, via an ATP-dependent step, to intracellular proteins targeted for degradation. The resulting tagged peptide is degraded in the proteolytic channel of the 26S proteasome. Ubiquitin is then cleaved from the target peptide to enable recycling (Fig. 4.8). Ubiquitin immunoreactivity is a prominent feature of the neuropathology of many neurodegenerative diseases,[40,41] where it is found as a component of various inclusion bodies. There is no evidence for a primary abnormality of the ubiquitin-proteasome pathway in these diseases, and it appears that ubiquitination is a consequence of the accumulation of abnormal proteins. UBIs in ALS are not detected by antibodies to the molecular markers that characterize many neurodegenerative disorders: tau, α-synuclein or polyglutamine,[42–45] and the substrate for ubiquitination is not currently known.

Bunina bodies

These eosinophilic bodies present in the soma of lower motor neurons were first described by Bunina in 1962.[46] They are found in the majority (86%) of ALS cases,[38] and are specific to the disease. They have been shown to be immunoreactive to the proteinase inhibitor cystatin C; however, their nature, origin and significance remain unclear[47] (Fig. 4.9).

Neurofilament conglomerate inclusions

Neurofilament conglomerate inclusions (NCIs, previously known as hyaline conglomerate inclusions) are larger and more prominent in conventional stains than UBIs and are detectable with silver stains. NCIs are immunoreactive to antibodies directed at both the phosphorylated and nonphosphorylated forms of heavy and medium chain neurofilament protein.[48] These stains also demonstrate that affected neurons lose the normal neurofilament cytoskeleton from the remainder of the soma[48] (Fig. 4.10). NCIs occur in a much lower proportion of cases than UBIs, and although they do arise infrequently in apparently sporadic cases, they are usually associated with familial ALS caused by pathogenic mutations I113T, A4V and H48Q of the SOD1 gene.[48–51] They have also been described in a few neurologically normal controls, and in

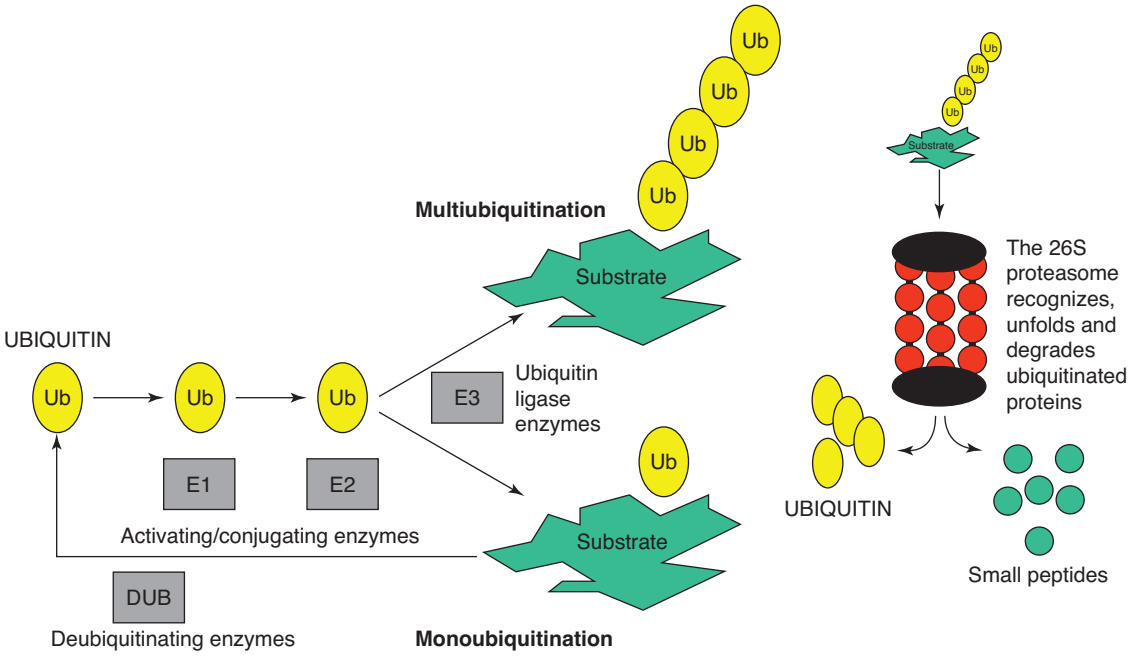

Fig. 4.8 The ubiquitin-proteasome system: the major protein degradation system in the cytoplasm.

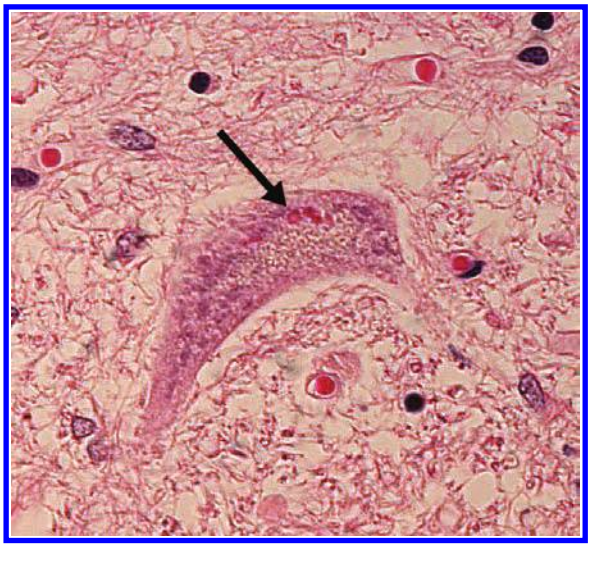

Fig. 4.9 Spinal lower motor neuron (anterior horn cell) showing Bunina bodies (arrow; H&E).

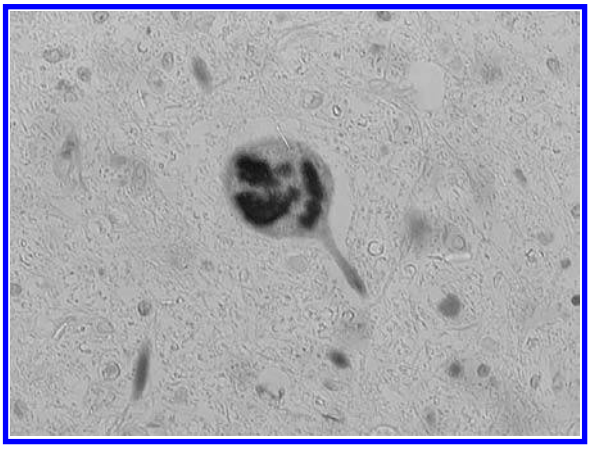

Fig. 4.10 Neurofilament conglomerate inclusion in spinal lower motor neuron in a case of I113T SOD1 FALS (ICC for SMI32 [nonphosphorylated neurofilament]). Reprinted from Motor Neurone Disorders, Pamela J Shaw and Michael J Strong (eds), page 35, copyright 2003, with permission from Elsevier.

patients with other neurological diseases, so they are less specific for ALS than UBIs.[52] As neurofilament protein is not a significant feature of UBIs, and NCIs have only been found in association with UBIs in one reported case (with the H48Q mutation), the molecular pathology of these neuronal inclusions suggests two distinct pathogenetic cascades.

Other neurofilament abnormalities in ALS

1. *Diffuse somatic phosphorylation of neurofilaments*. In normal neurons, the somatic neurofilaments are predominantly nonphosphorylated, while axonal neurofilaments have much higher levels of phosphorylation. Several authors have reported a diffuse increase in neurofilament phosphorylation affecting the soma of spinal motor neurons in ALS.[28,53–56]
2. *Globules and spheroids*. Axonal swellings in the anterior horn have been described in ALS. These 'spheroids' and 'globules' are composed of abnormally orientated conglomerations of neurofilaments, and are usually rich in phosphorylated epitopes. They generally resemble fusiform swellings in serial sections, and are presumed to represent focal abnormalities of axonal cytoskeletal regulation, with failure of axonal transport.[28] The lesions are not disease-specific, and are present in normal subjects, although the numbers of spheroids may be increased in ALS.[52–54] Spheroids have been described in the soma of spinal motor neurons,[57–59] and appear similar to NCIs using either immunochemistry, or electron microscopy, suggesting that the same disorders of cytoskeletal function may underlie both types of structure. Spheroids, unlike NCIs, are composed exclusively of phosphorylated epitopes, although this may reflect the site of their aggregation, as the axon contains very little nonphosphorylated neurofilament protein.[28]

Upper motor neuron pathology in ALS

A cardinal feature of the pathology of ALS is axonal loss from the descending pyramidal motor pathway, associated with secondary myelin pallor and gliosis of the corticospinal tracts (giving rise to the lateral sclerosis originally described by Charcot). Pallor in myelin stains is most prominent in the cervical cord and medullary pyramids, and in many cases is not demonstrable above the level of the medulla, including cases with no discernible motor cortex pathology. This finding suggests that UMN changes in ALS arise from an axonopathy, with distal denervation due to axonal loss preceding somal degeneration and loss of pyramidal cells from the cortex.[28]

In the motor cortex, pathological changes are highly variable, even in patients with well established clinical UMN involvement. Severely affected cases will usually show a reduction in the population of giant pyramidal neurons (Betz cells) in the motor cortex, either due to loss of neurons, or a reduction in their size so that they are indistinguishable from neighboring pyramidal cells. Intracellular inclusions, including UBIs, have not been convincingly described in Betz cells.[28] The motor cortex may show variable astrocytic gliosis in the gray matter and underlying subcortical white matter. Microglial activation, observed using immunochemistry against CD68[37] and HLA-DR antigens[60] is also seen in the corticospinal tract of the brain and spinal cord (Fig. 4.11) and motor cortex (Fig. 4.12).

Muscle pathology

Skeletal muscle atrophy occurs in ALS due to denervation, with clusters of angular atrophic fibers, which display fiber-type grouping. These features are a consequence of serial denervation and reinnervation, which arises from collateral sprouting of intramuscular axons.[28]

Pathological features of PLS and PMA

The pathological features of 11 patients with PLS have been described since 1977.[22,25,28,61–66] The most characteristic and consistent features seen are atrophy of the prefrontal gyrus, with associated loss of Betz cell somata, and pallor and atrophy of the lateral corticospinal tracts. Seven cases predate the use of ubiquitin immunochemistry, but of these, three demon-

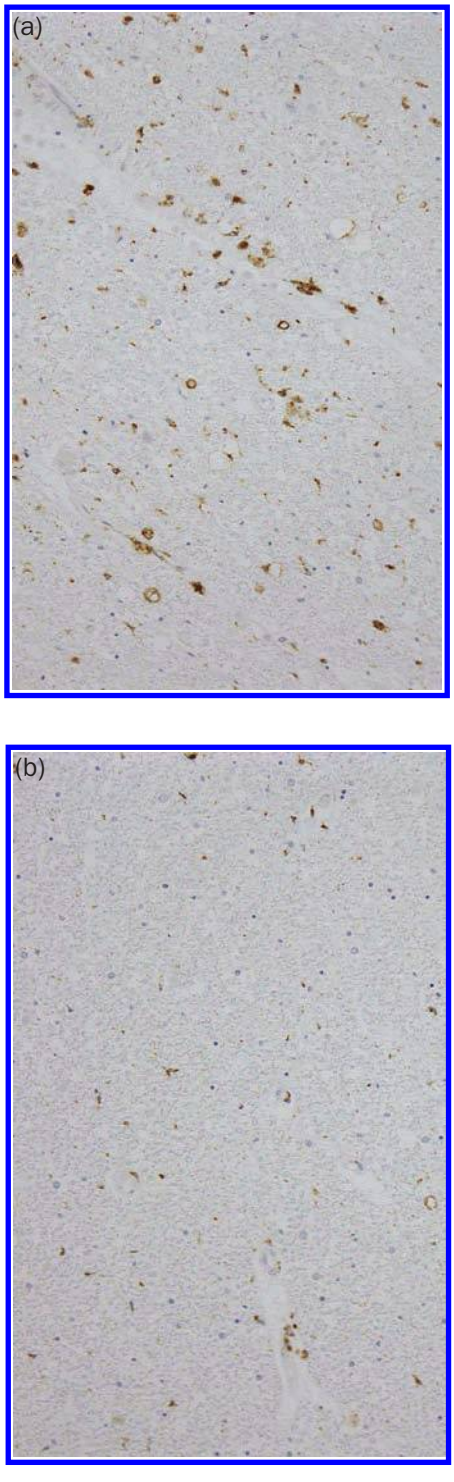

Fig. 4.11 Microglial activation in the lateral corticospinal tract in ALS (a; ICC for CD68) contrasts with appearances in the unaffected dorsal column (b; ICC for CD68).

strated eosinophilic inclusions within the anterior horn cells or the cranial nerve nuclei.[62–64] In two of the four cases in which ubiquitin immunochemistry was carried out, typical UBIs were seen in a few LMNs at autopsy,[65,66] and gliosis of the anterior horns was described in two cases.[22,65] An additional important feature of these cases is the presence of UBIs in the cerebral cortex in a distribution typical of ALS dementia cases,[28,66] suggesting that PLS may merge into the spectrum of ALS dementia.

A pathological study of 14 patients with the clinical phenotype of PMA demonstrated typical UBIs in the spinal cord or bulbar motor neuron groups in 12 patients.[37] Of the two patients in whom UBIs were not identified, one was an elderly patient with a 10-year history of an indolent progressive weakness, and the second was a familial patient with an unusual family history.[67] UBIs are not seen in either Kennedy's disease or SMA.[28,68] Of the 12 cases with UBIs, 7 were also shown to have subclinical corticospinal tract involvement demonstrated by immunostaining for active microglia and macrophages.

The pathological findings of occasional abnormalities of the lower motor neurons in PLS, and of corticospinal tract involvement in PMA, support the clinical evidence of overlap between these conditions and ALS.[69,70] Ubiquitinated inclusions are the characteristic pathological feature of ALS, PLS and PMA, suggesting that these disorders share common pathophysiological mechanisms, and that PLS and PMA should be considered part of the spectrum of ALS.

THE CLINICAL AND PATHOLOGICAL SPECTRUM OF EXTRAMOTOR FEATURES IN ALS

ALS is traditionally considered to be a pure motor disorder, which spares sensation, cognition and the autonomic functions. However, there is increasing evidence that, despite the relative vulnerability of motor neurons to the degenerative process in ALS, other neuron types are affected. ALS is now regarded as a multisystem neurodegenerative disorder in which the earliest and most severe

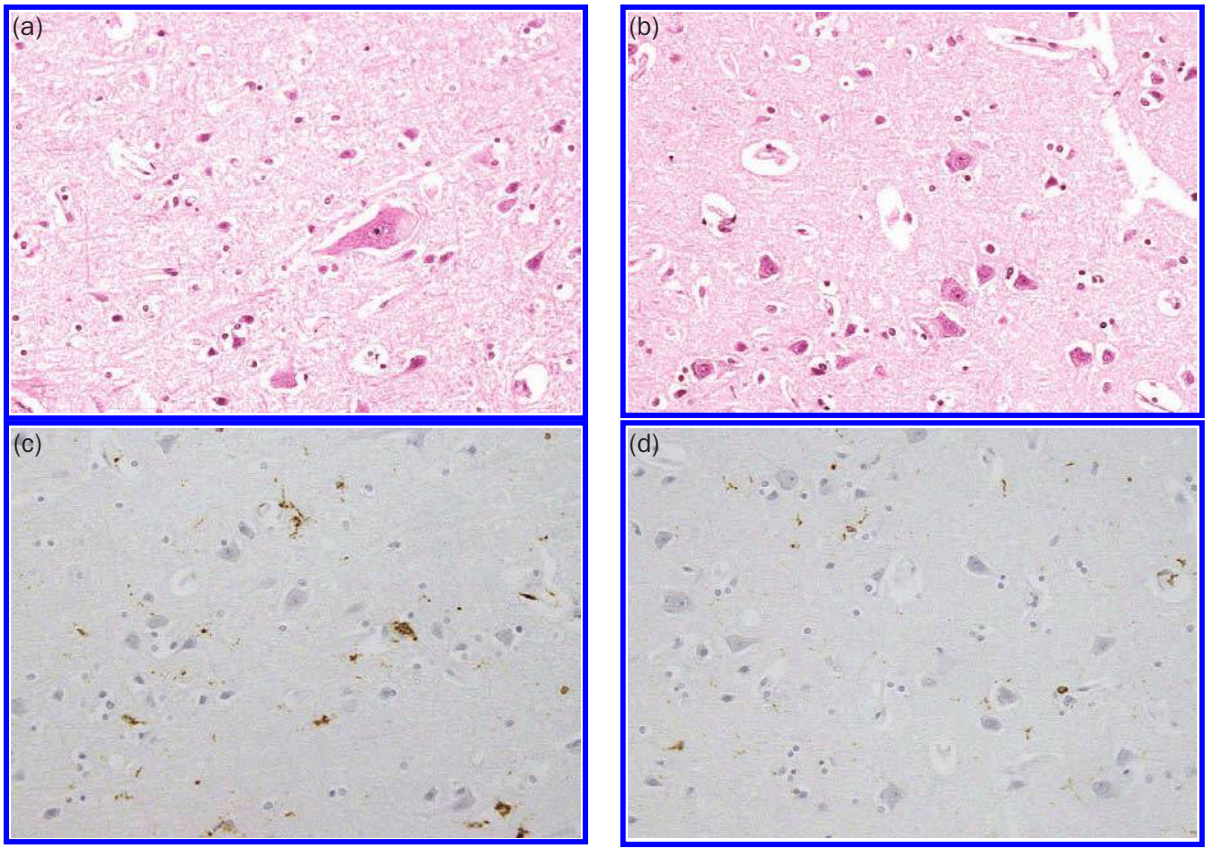

Fig. 4.12 Motor cortex with intact Betz cell (a; H&E) showing modestly increased prominence of activated microglia (b; ICC for CD68). In contrast the cortex of Brodmann area 6 (c; H&E; premotor cortex) shows minimal evidence of microglial activation (d; ICC for CD68).

degeneration tends to involve motor neurons. In most patients, the evolution of motor dysfunction is lethal before the development of overt CNS pathology in other regions, although occasionally ALS patients may spontaneously develop a severe multisystem degeneration.[71] In those who are treated with ventilation after the onset of respiratory failure the duration of disease is prolonged, and features of extramotor system involvement become particularly prominent. In these patients, the 'total manifestations' of ALS are seen.

Extramotor pathology has been a recognized feature of ALS for many years, although the extent and nature of these changes was unclear prior to the advent of molecular biology, as pathological changes of gliosis and neuronal loss are subjective, and difficult to ascribe specifically to a disease process. The use of ubiquitin immunochemistry has introduced more precision into the identification of extramotor regions involved in the degeneration caused by ALS. However, problems of interpretation remain, largely due to 'physiological' ubiquitin immunoreactivity that appears to be a normal feature of the aging brain, particularly of the hippocampus, frontal cortex, and substantia nigra.[72] The recent development of a new marker which also labels ubiquitinated lesions of age-related neurodegenerative disease, but not age-related physiological ubiquitinated material may circumvent these difficulties.[73] This new marker is p62, a transcriptional regulator with a ubiquitin-binding domain.

Manifestations of prolonged disease

Patients who are treated with invasive ventilation after the onset of respiratory failure are initially able to maintain communication in the presence of tetraparesis and anarthria, through eye move-

ments, which are typically spared in ALS. However, they later develop limitation of upward eye movements, followed by loss of voluntary control of the ocular muscles, and become totally 'locked-in'.[74,75] They also lose control of external sphincters, and develop decubiti, features that are not seen in typical ALS.[75–78] Electroencephalograms (EEGs) performed at later stages of disease show diffuse EEG slowing.[76] Magnetic resonance imaging (MRI) of patients with initially normal cognitive function who were maintained on invasive ventilation demonstrated progressive atrophy, which included the frontal and temporal lobes, precentral gyrus, postcentral gyrus, anterior cingulate gyrus, and corpus callosum.[74]

Mizutani et al.[75] give the following description of the clinical course of an ALS patient on long-term ventilation:

> A 51-year-old man without a family history of motor neuron diseases had gradually developed limping in his left leg and difficulty in talking and swallowing at the age of 38 years ... At the age of 43, he suffered an episode of respiratory arrest and hypotension after an esophagostoma operation for tube feeding. He was intubated, and returned to a normal mental status and his previous neurological deficits 2 days later. Subsequently, he remained on a respirator. At about this time, his eyes showed some oscillation to the right or left side alternately on moving upwards ... After 3 years survival on the respirator, he displayed progressive limitation of his extraocular movements ... moderate to marked slow pursuit eye movements with inability to perform saccadic eye movements, mild limitation of the eye movements during lateral and upward gazes with inability to move the eyes downwards and converge, no nystagmus and preserved light reflex of the pupils. In addition, he had extensive shallow decubitus ulcers on the back, which became persistent. At the age of 47, he occasionally exhibited urinary retention and constipation. When aged 49, he could not move his eyes or skeletal muscles of the face and 4 extremities, although doll's eye phenomenon was present ... He lapsed into 'a totally locked-in state'. At the age of 50, he lost the doll's eye phenomenon. Polysomnography revealed the presence of stage 1–4 sleep without any stage REM sleep ... His stage 2 sleep changed to an awake pattern with loud stimuli. The patient died at the age of 51, some 8 years after he had been placed on the respirator.
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> (Reprinted from[75] with permission from Elsevier.)

Reports of the neuropathology of patients with such prolonged disease document widespread CNS degeneration.[75–78] The structures involved include the oculomotor nuclei and nucleus of Onufrowitz, which are typically spared in ALS, and the sensory and autonomic nervous systems, with degeneration of the dorsal column of the spinal cord, medial lemnisci, thalamus and intermediolateral nucleus. Cerebellar pathways, including Clarke's column, the spinocerebellar tract, olivocerebellar tracts and inferior and superior cerebellar peduncles are involved. There is degeneration of the dentatorubral and pallidoluysian systems, the subthalamic nucleus and substantia nigra, although the caudate and putamen are relatively spared. Involvement of the brainstem reticular formation and locus coeruleus is also seen. A distribution of neuropathological lesions that resembles that seen in progressive supranuclear palsy, with degeneration of the periaqueductal gray matter, pontine tegmentum, superior colliculi, medial longitudinal fasciculi and vestibular nuclei may correlate with the early eye movement abnormalities seen in these patients.

Cognitive impairment

Frontotemporal dementia

Frontotemporal dementia (FTD) encompasses a range of clinical syndromes that result from focal atrophy of the frontal and anterior temporal regions, and three major clinical manifestations are recognized. In frontal variant FTD (fvFTD), there is prominent personality change and conduct disorder, and patients may become disinhibited or apathetic with emotional blunting, and loss of insight. Behavior may become ritualized or stereotypical, and patients may change their eating pattern, often developing an obsession with food. In contrast to Alzheimer's disease, there is preservation of visuospatial

function and memory. Two syndromes of progressive language dysfunction are seen with FTD: primary progressive aphasia (PPA) is characterized by effortful speech production with phonological and grammatical errors, and word retrieval difficulties, progressing to mutism. In semantic dementia (SD), impairment of naming and word comprehension occurs in the context of fluent, grammatical speech output.[79–81] There is overlap between these clinical presentations, as patients with PPA or SD may develop subsequent deterioration in personality and behavior,[82] while FTD is often accompanied by language abnormalities.[83,84]

FTD and ALS

There have been sporadic case reports of associations between ALS and dementia since the nineteenth century. This association has now been documented more systematically, first in Japan and since the 1980s in Caucasian patients. Approximately 5% of patients with ALS are thought to show overt features of FTD (ALS-FTD),[85] although a recent study suggested a higher prevalence of up to 15% in sporadic ALS.[86] Cognitive dysfunction may precede, follow, or coincide with the motor deficit. The most common clinical picture of FTD in association with ALS is that of progressive deterioration in personality and behavior (fvFTD),[87] but PPA is also described.[82,84,87–90]

Cognitive impairment in ALS patients without dementia

ALS patients without overt dementia demonstrate subtle defects of frontal lobe function,[91–97] which may be under-recognized without detailed neuropsychological testing, due to the difficulty in assessing cognitive function in patients with bulbar dysfunction and advanced motor deficits. A recent study demonstrated that 50% of 280 patients with sporadic ALS had features of frontal lobe dysfunction.[86] Cognitive impairment may be more common in patients with PLS or predominant UMN signs,[98,99] and in those with bulbar involvement.[93,94,97] Functional imaging studies have supported these clinical findings, showing a reduction in regional cerebral blood flow or glucose metabolism in the frontal cortex and limbic system of ALS patients, which is more pronounced in those patients shown to have subclinical defects of frontal lobe function, and most marked in patients with ALS-FTD.[91–93,100–104] Imaging studies have also demonstrated atrophy of the frontal lobes in nondemented ALS patients.[105]

Pathological correlates of cognitive impairment in ALS

Patients with ALS and dementia (ALS-FTD) have both the characteristic motor system UBIs of ALS, together with cerebral pathology, which comprises small globular UBIs of the dentate granule cells, and a variable component of neocortical ubiquitinated neurites and small neuronal UBIs[106–111] (Fig. 4.13). Other limbic structures, including the amygdala and parahippocampal gyrus, may also show ubiquitinated pathology.[112,113] Retrospective pathological studies suggest that 20–50% of nondemented ALS patients have similar pathology, although the severity and distribution tends to be less extensive.[107,110,112–115]

In patients who present with FTD without ALS, the pathological correlates of FTD are heterogeneous, with three broad subdivisions recognized: tau-positive pathology (Pick's disease, corticobasal degeneration and progressive

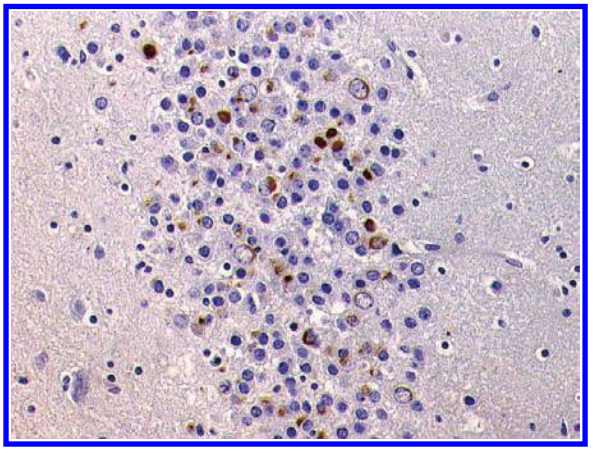

Fig. 4.13 Dentate gyrus granule cell layer in ALS-dementia showing numerous intraneuronal ubiquitinated inclusions (ICC for p62).

supranuclear palsy), dementia lacking distinctive histology (DLDH), and ubiquitin-positive inclusions (motor neuron disease-inclusion dementia, MND-ID).[79,81,87] The latter group show identical cerebral pathological changes to patients with FTD-ALS. Patients who present with the language variants of FTD show pathological changes predominantly affecting cerebral cortical regions involved in speech pathways.[82,88,116,117] There is evidence that MND-ID represents a 'forme-fruste' of FTD-ALS. Patients who have had FTD for many years may develop motor neuron degeneration,[118] while pathological examination of the spinal cord or brain in patients with MND-ID has shown occasional lower motor neuron UBIs,[119–122] or fragmentation of the Golgi apparatus in lower motor neurons of the brainstem and spinal cord, which although not disease-specific, is a recognized feature of motor neurons in ALS.[123]

The degree of overlap in pathological findings, neuropsychological deficit and imaging studies in classical ALS without dementia, MND-ID and ALS-FTD suggests that they represent a spectrum of clinical disease with a common pathological substrate.

Extrapyramidal features

Parkinsonism

Parkinsonism is described in cases of sporadic ALS, and occurs more frequently in cases of ALS with dementia.[124–126] The prevalence of parkinsonism in ALS may be underestimated, as extrapyramidal features can be obscured in patients with weakness, wasting and spasticity of muscles. Subclinical defects in dopaminergic transmission were demonstrated by PET scanning in patients with sporadic ALS, without symptoms of extrapyramidal disease.[127]

The following case description of ALS with extrapyramidal symptoms is taken from Qureshi et al.[126]

> A 68-year-old woman presented with 3 months of progressive weakness and pain in her left upper extremity. Additionally, her family observed bradykinesia, gait difficulty and slurred speech. On initial examination, cognitive functions were intact. Marked generalized bradykinesia and rigidity were most prominent in the left upper extremity but with no tremor. Bradykinesia and rigidity precluded accurate strength testing. Fasciculations were noted in all extremities. There was generalized hyperreflexia with the exception of hypoactive ankle jerks. Mildly reduced sensation in distal lower extremities was present ... She walked with a slow shuffling gait and had postural instability with a tendency to retropulse when pulled backward ... Electromyographic studies revealed denervation with fibrillations in 3 limbs. Over the next 3 months, the rigidity continued to increase, despite increasing doses of levodopa. The patient developed progressive dysphagia and died from aspiration pneumonia 18 months after onset.
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Disorders of eye movement

Supranuclear ophthalmoplegia, including limitation of ocular movement, slow ocular movement and spasmodic gaze fixation, is described in ALS. Although the majority of these patients develop this manifestation after a prolonged disease course with invasive ventilation, it is also seen in 'natural disease'.[74–76,87,128] Difficulty initiating eyelid opening, with preserved reflexive eyelid movements, often referred to as 'eyelid apraxia', is also seen in patients with ALS, and may be associated with supranuclear vertical gaze impairment.[129,130]

Pathological correlates of extrapyramidal features

Several studies have described atrophy of the neostriatum, substantia nigra, globus pallidus and corpus Luysii in ALS, sometimes in association with typical UBIs.[108,114,119,120,124,131,132] Spherical or crescentic UBIs in the cytoplasm of small neurons in the neostriatum of patients with ALS[113,133,134] should be distinguished from skein-like inclusion in large neurons, which are a feature of normal aging.[133,135] Involvement of

subcortical nuclei is more commonly seen in patients with dementia,[71,113,133,136] and has been described in patients with and without extrapyramidal features, although the lesions are more severe and widespread in patients with extrapyramidal features compared with those with ALS-FTD alone.[134]

Corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are extrapyramidal syndromes which clinically overlap with FTD. CBD most commonly presents with progressive asymmetrical rigidity and apraxia, while PSP is characterized by progressive axial rigidity, bradykinesia, vertical gaze palsy, and dysarthria. Patients with CBD or PSP may also develop progressive aphasia or a behavioral frontal lobe syndrome.[108,137] Similarly, extrapyramidal symptoms are recognized in patients with FTD.[79,87] Patients presenting with bradykinetic-rigid syndromes, sometimes in association with frontal cognitive impairment, which fulfilled diagnostic criteria for PSP or CBD, have recently been shown on post mortem to have hippocampal and neocortical UBIs typically seen in MNDID, in addition to basal ganglia UBIs.[87,138,139] This further widens the clinical spectrum of disease associated with ubiquitinated pathology.

Sensory impairment

Patients with ALS not infrequently complain of nonspecific sensory phenomena, such as tingling in the fingers. Sensory examination is usually normal, however, nerve conduction studies and somatosensory evoked potentials (SSEPs) reveal the presence of abnormalities in peripheral and central sensory pathways in up to 60% of patients.[140–148] There are isolated case reports of more profound sensory involvement in association with ALS.[149]

The ascending sensory pathways of the dorsal column are commonly affected in ALS. In the Japanese literature, the prevalence of dorsal column pallor in familial disease is emphasized, with the concept of 'familial ALS with posterior column involvement'. However, more recent work suggests that this change is detectable at autopsy in up to 50% of all sporadic ALS cases.[37] There is also evidence of degenerative changes in peripheral sensory nerves, and loss of large afferent nerve fibers.[150,151]

Cerebellar pathways

Cerebellar involvement in ALS is not clinically recognized, although late involvement of these pathways could go undetected in the presence of severe weakness. Although not clinically apparent, degeneration of the spinocerebellar pathway, both in terms of cell loss from the thoracic nucleus of Clarke, and of pallor of ascending spinocerebellar pathways, is a relatively frequent finding in sporadic ALS.[152–154] Furthermore, there are isolated case reports[155,156] of patients with cerebellar ataxia, supranuclear ophthalmoplegia and amyotrophy. In one of these patients,[155] autopsy revealed pathological changes consistent with ALS, and degeneration of the spino-ponto-cerebellar pathway, but ubiquitin immunochemistry was not performed.

THE GUAM COMPLEX

In the 1950s a pocket of very high incidence of ALS was identified on the Pacific island of Guam, where the indigenous Chamorro people had a rate of the disease about 50–100 times that of western populations. In 1961, Hirano identified a unique neurodegenerative condition amongst the same population, termed parkinsonism-dementia complex (PDC).[157] Affected individuals develop a severe dementia, and rigido-akinetic parkinsonism with marked postural deformities. Hyperreflexia and spinal muscular atrophy, developing mainly in the distal extremities, are often observed. A familial appearance is seen among some PDC cases, and this may also include ALS and vice versa. The occurrence of PDC and ALS in a geographically isolated population in similar age groups, and with overlap in symptomatology and familial aggregation led to the suspicion that the two diseases were related.[158]

The etiology of PDC and Guamanian ALS is unknown. Detailed pedigree analysis and the search for specific genetic markers have failed to yield a satisfactory genetic explanation, despite apparent familial clustering of the diseases. Several observations support an environmental

etiology, including the fact that immigrant Filipino populations are susceptible to the diseases, and that there is a trend of increasing age of onset of the diseases over time. The leading hypothesis relates to ingestion of an environmental toxin present in the seed of the false sago palm, *Cycas circinalis*.[159]

ALS-PDC of Guam appears pathologically to be a tauopathy, characterized by the formation of neurofibrillary tangles. Variation in the anatomical distribution of pathology accounts for the varying clinical presentations, with tangles predominantly seen in the motor system in Guamanian ALS.[159]

THE CLINICAL AND PATHOLOGICAL SPECTRUM OF FAMILIAL ALS (FALS)

Patients with ALS report a family history of the disease in about 5–10% of cases, although this figure varies between reported series.[160] The most commonly reported pattern of inheritance is dominant, with complete penetrance, although recessive or X-linked inheritance occurs in some pedigrees. Linkage studies in ALS are rendered difficult by age-dependent onset in adults, short disease duration, heterogeneity of presentation and misdiagnosis. Linkage to 13 different chromosomal locations has been established in familial ALS, and for 6 of these, the underlying genetic defect has been identified (Table 4.2). The neuropathology of relatively few of the genetic subtypes of ALS has been characterized, and the pathological features of alsin-related ALS, the senataxin, VAPB and dynactin mutations have not yet been described.

Gene mutations have also been identified in some patients with sporadic ALS. The angiogenin gene contains a single nucleotide polymorphism (SNP), which has significant association with the disease. A novel mutation in the angiogenin gene was subsequently identified in two patients with sporadic ALS.[161] Angiogenin is of particular interest, as it has similar functions to vascular endothelial growth factor (VEGF), which has recently been identified as having functional significance in the survival of motor neurons.[162,163]

Adult-onset dominant ALS

Familial ALS with adult onset is clinically indistinguishable from sporadic ALS in individual cases. In all, 20% of cases are caused by mutations

Table 4.2 Familial ALS

	Age of onset	*Inheritance*	*Chromosome*	*Gene*
ALS1	Adult	Dominant	21q22.1	SOD1
ALS2	Juvenile	Recessive	2q33	ALSIN
ALS3	Adult	Dominant	18q21	
ALS4	Juvenile	Dominant	9q34	Senataxin
ALS5	Juvenile	Recessive	15q15.1-q21.1	
ALS6	Adult	Dominant	16q12	
ALS7	Adult	Dominant	20ptel-p13	
ALS8	Adult	Dominant	20q13.33	VAPB
ALS-X	Adult	Dominant	Xp11-q12	
ALS-dementia complexes				
ALS-FTD	Adult	Dominant	9q21-22	
ALS-FTD	Adult	Dominant	9p21.3-13.3	
ALS-PD-dementia	Adult	Dominant	17q21-22	Tau
MND-ID	Adult	Dominant	17q21-22	Not tau-related
DLDH and ALS	Adult	Dominant	3	CHMP2B

ALS, amyotrophic lateral sclerosis; DLDH, dementia lacking distinctive histology; FTD, frontotemporal dementia; MNDID, motor neuron disease-inclusion dementia; PD, Parkinson's disease.

in the gene encoding the free radical scavenging enzyme superoxide dismutase (SOD1).[164] More than 100 mutations have now been identified, the majority of which are missense mutations. SOD1 is a ubiquitously expressed metalloenzyme whose major function is to convert intracellular superoxide free radicals to hydrogen peroxide. Mutant SOD1 exerts its deleterious effects through a toxic gain of function, although the nature of this toxicity, and why motor neurons are especially vulnerable to injury has not been established with certainty.

Certain mutation-specific clinical phenotypes are recognized.[160] The A4V mutation causes rapid disease progression, and a progressive muscular atrophy phenotype is seen with A4V and D101N. Autonomic failure has been reported in cases with G93S and V118L mutations, while prominent sensory symptoms may delay diagnosis in V14G, E21G, H46R, D90A and E100G mutations. D90A is recessively inherited in Scandinavian populations, implicating the existence of a co-inherited protective or modifying gene in this population.

The pathology of SOD1 mutations

There are now more than 100 SOD1 mutations described, and neuropathological correlation is available for relatively few of these. The current literature highlights the similarity of neuropathological changes seen in SOD1-related ALS to the sporadic disease, and all the neuronal inclusion bodies described in sporadic ALS are also seen in FALS. Although individual cases are usually indistinguishable, some mutation-specific features are described.

Corticospinal tract involvement

Two SOD1 mutations appear to be associated with relative preservation of the corticospinal tract: A4V[165] and D101N.[166]

Intraneuronal inclusions

SOD1 mutations I113T, A4V and H48Q[48–51,167] are distinguished by the presence of neuronal NCIs, and in the case of I113T, by a lack of UBIs. UBIs are reported in association with other SOD1 mutations,[51,168,169] and in conjunction with NCIs in the H48Q mutation.[51]

In SOD1 transgenic mice, there is prominent accumulation of SOD1 in affected tissues. There are reports of similar accumulation of SOD1 in 'Lewy-like hyaline inclusions' in human FALS, in association with L126S,[170] D101Y,[171] 126del2,[172] H46R,[173] and A4V[174] SOD1 mutations. The morphology and immunoreactivity of these lesions in the human material is different from typical skein-like or compact UBIs in that they are distinctly hyaline rather than fibrillary, rounded, and show a concentric pattern with an apparently denser core. These ubiquitin and SOD1 immunoreactive structures have also been described in a familial case of ALS without a SOD1 mutation,[175] and in sporadic cases of ALS.[176] However, other neuropathological studies of large numbers of sporadic ALS patients have not identified SOD1 immunoreactive intraneuronal inclusions.[48]

Astrocytic inclusions

Astrocytic hyaline inclusions are also described in both human FALS[172,173,175] and in animal models of SOD1 FALS. In the transgenic SOD1 mouse models, these lesions are often more prominent than those in neurons.[177,178]

Non-SOD1 FALS

Mutations in vesicle-associated membrane protein B (VAPB), encoding a protein which has functions in membrane transport, were recently identified in a Brazilian family with ALS8, a slowly progressive disorder characterized by fasciculations, cramps and postural tremor. The same mutation was subsequently identified in six further families with different phenotypes of motor neuron degeneration, including classical rapidly progressive ALS.[7] Linkage has been established in other pedigrees with familial autosomal dominant ALS without distinguishing clinical features, to chromosome 16q12[179] and to chromosome 18q21.[180]

Hereditary motor neuronopathy (HMN) is a group of familial neurodegenerative conditions that predominantly affect the lower motor neurons, although mild pyramidal features are seen in some subtypes. There is therefore clinical overlap between HMN and familial ALS with lower motor neuron predominance. Several

mutations have been identified in HMN patients, including mutations in immunoglobulin mu-binding protein 2 (IGHMBP2), glycyl tRNA synthetase (GARS), the Berardinelli-Seip congenital lipodystrophy gene (BSCL2), and heat shock proteins HSP22 and HSP27. Although some of these mutations have been shown to underlie other neurodegenerative diseases, including Charcot-Marie-Tooth disease, and hereditary spastic paraparesis, they have not been described in typical FALS.

A mutation in the P150 subunit of dynactin (DCTN1) was recently identified in a single family with a hereditary motor neuronopathy of unusual slowly progressive phenotype that included presentation in early adulthood with respiratory difficulties, facial weakness, and weakness and atrophy of the hands.[3] The dynactin–protein complex is required for dynein-mediated retrograde axonal transport of vesicles and organelles along the microtubule system. Mutations of the p150 subunit of DCTN1 were subsequently identified in patients with familial ALS and FTD, and one case of apparently sporadic ALS.[181,182]

Juvenile ALS

Two mutations have been identified that cause juvenile ALS, while a third pedigree with recessive inheritance and predominant lower motor neuron signs is linked to chromosome 15q.[183] Alsin is a protein of unknown function which contains three putative guanine nucleotide exchange factor domains. Mutations in this protein have been identified in autosomal recessive juvenile ALS, in which UMN signs predominate,[4,5] and in several other juvenile-onset neurodegenerative conditions, including hereditary spastic paraplegia.[184–186] Three different missense mutations have been identified in senataxin, a putative DNA/RNA helicase, in pedigrees with dominant juvenile-onset indolent ALS.[6] The neuropathology of patients with juvenile ALS has not been described.

Familial FTD

In addition to the ubiquitinated cytoplasmic inclusions in the neocortex and dentate granule cells of the hippocampus, which are characteristic of sporadic ALS-FTD, intranuclear inclusions have been identified in the neocortex, striatum and hippocampal dentate granule cells in patients with familial MND-ID, and less commonly in patients with familial ALS-FTD.[187–189]

Familial ALS-FTD and MND-ID are genetically heterogeneous conditions, which have been linked to several chromosomal loci. FTD with parkinsonism is linked to chromosome 17q21, and in most cases is caused by mutations in the microtubule binding domain coding or splicing sequences of the microtubule-associated protein tau gene.[190,191] At autopsy, numerous neuronal and glial inclusions of aggregated filaments of hyperphosphorylated tau proteins are seen, associated with neuronal loss. Some kindreds with FTD and parkinsonism also develop amyotrophy, and in these patients, degenerative changes of the motor cortex, or motor neurons of the brainstem and spinal cord are seen.[192–194] This association of FTD, parkinsonism and amyotrophy with tau pathology has considerable similarities to the Guam ALS/PDC complex.

In several families linked to the 17q21 region, no tau mutations were found, suggesting that a second gene close to tau or noncoding regions of the gene play a role in the pathogenesis of the condition. In one of these families, in which motor neuron disease was a prominent feature, tau and α-synuclein inclusions were seen in the temporal lobes, limbic system and brainstem, although the spinal cord was not examined, and ubiquitin immunochemistry not described.[195] In a second family with the phenotype of FTD, abundant ubiquitin-positive, tau- and α-synuclein-negative inclusions were seen in the frontotemporal cortex and dentate gyrus.[187]

ALS-FTD has been linked to chromosome 9q21-22 in one pedigree,[196] and in a large Scandinavian family, in which ALS and FTD segregated in the same kindred, both diseases were recently found to be linked to chromosome 9p21.3-p13.3.[197] FTD with no distinctive pathology has been linked to chromosome 3, and mutations subsequently found in the acceptor splice site of exon 6 in CHMP2B (charged multivesicular body protein 2B), a

component of the endosomal ESCRT III complex.[198] Although these patients did not show ubiquitinated pathology, a link to ALS was established by the recent finding of novel heterozygous mutations in the coding regions of CHMP2B in two patients with ALS, one of whom also presented a frontal lobe syndrome (unpublished observations). In one of the ALS patients, previously unrecognized oligodendroglial inclusions were revealed in the motor cortex by p62 staining, in addition to classical UBIs within the spinal cord.

CONCLUSION

ALS is a neurodegenerative disorder that primarily affects upper and lower motor neurons, causing progressive paralysis of the muscles of the limbs and bulbar regions, and the respiratory muscles. In a small proportion of patients, gene defects have been identified that cause motor neuron degeneration, but in the majority of both sporadic and familial patients, the etiology of the disease is unknown.

UBIs are now recognized as the molecular pathological change that characterizes ALS, analogous to Lewy bodies in Parkinson's disease, or senile plaques and neurofibrillary tangles in Alzheimer's disease. This has allowed a group of clinically related motor system disorders – ALS, PMA, PLS, PBP, and ALS-FTD – to be fitted into the framework of a common molecular pathology. The clinical correlates of this pathology include MNDID, progressive supranuclear palsy and corticobasal degeneration, conditions with no clinical evidence of motor neuron degeneration. UBIs have been identified in many structures outside the motor system, like the hippocampus and basal ganglia, confirming the clinical impression that ALS patients can present a spectrum of extramotor neurological impairment, such as FTD, parkinsonism, and subtle changes in sensation. The use of ubiquitin immunochemistry to examine extramotor regions in ALS patients has expanded the concept of ALS as a multisystem disorder, in which motor neurons are relatively vulnerable to the degenerative process.

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5

Identification and categorization of frontotemporal impairment in ALS

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INTRODUCTION

An association between frontotemporal lobe dementia (FTLD) and amyotrophic lateral sclerosis (ALS) has been recognized for the past several decades,[1–3] with motor neuron signs developing among FTLD patients,[4] and ALS patients being diagnosed with comorbid FTLD. Among the ALS population, the frequency of comorbid FTLD has been believed to be a rare one, with rates believed to be below 5%. Recently, several groups have questioned whether the rates are indeed as low as once believed[5–7] and, more fundamentally, whether the cognitive changes seen in ALS patients are better conceptualized as a broad continuum of frontotemporal impairment that includes FTLD at the extreme end of the spectrum.[8]

Five recent advances have emerged in the field of cognitive change in ALS, and these observations will be the focus of this chapter: (1) the frontotemporal impairment seen in ALS patients is not a rare event consisting of full-blown dementia as was once thought, but appears to lie on a spectrum, with a wide percentage of patients showing varying signs of pathology; (2) specific, definable subtypes of patients have been proposed, to identify patients with milder forms of frontotemporal impairment; (3) standardized neuropsychological batteries are being shared among laboratories to facilitate inter-investigator comparisons; (4) brief screening batteries are being explored to rapidly identify ALS patients who show symptoms of frontotemporal impairment; and (5) the presence of frontotemporal changes in ALS patients negatively affects their course of motor neuron disease.

An association between dementia and ALS was first noted in the late 1800s and has subsequently been reported by many investigators.[3] Both familial and sporadic ALS patients exhibit signs of frontal lobe deterioration, including personality, behavior, planning, organization, and language dysfunction. Among patients with FTLD presenting to a dementia clinic, 15% met criteria for a definitive ALS diagnosis and an additional 30% had more subtle signs suggesting possible ALS.[4] Conversely, a percentage of ALS patients possess comorbid FTLD, most often emerging before their motor neuron symptoms. It is yet unknown what common

mechanism may underlie the co-occurrence of ALS and FTLD, but the field exploring this question has become an active and exciting area of research in the past decade.

Evidence from fields as broad as pathology, structural imaging, PET, SPECT, and neuropsychology suggest that the frontotemporal impairment among ALS patients lies on a broad spectrum, with approximately half of the patients displaying at least mild abnormalities. A consistent finding has emerged: the pathological signs, cerebral atrophy, blood flow decrements, neurotransmitter decrease and neuropsychological impairment reveal the same pattern of abnormalities whether the patient shows very mild, subclinical changes, moderate change that is perceived by the patients and families, or full-blown dementia, suggesting that a frontotemporal degenerative process among ALS patients is not the rare event that was once thought.

THE CONTINUUM OF COGNITIVE AND BEHAVIORAL IMPAIRMENT IN ALS

'Executive functioning' is a term used to describe the complex cognitive process that requires the frontal lobe to integrate input from multiple cortical systems. Planning, organizing information mentally, shifting attention, inhibiting behavior, and negotiating social mores are all examples of executive functioning. Historically it was thought that less than 5% of ALS patients possessed such frontal lobe deficits, as caused by full-blown FTD. In the past 20 years, however, dozens of studies have documented the presence of executive functioning deficits among a sizable percentage of ALS patients.[9] Frequently, these data reveal that nondemented patients possess the same executive function deficits seen in ALS patients with associated FTLD, but simply to a milder degree, suggesting a continuum of involvement.

Rates of executive function deficits among nondemented ALS patients range from 22%[5,7,10] to 35%.[11] Specific deficits consist of verbal and design fluency loss, poor sustained attention, poor verbal reasoning, impaired set-shifting, poor response inhibition, loss of visual attention, decreased initiation of random movements on a joy-stick task, and poor problem-solving and judgment on tests such as the Wisconsin Card Sorting Test. The most common deficit documented in ALS patients is a deficit in verbal fluency, and this pattern is seen in both demented and nondemented patients.

Neurobehaviorally, ALS patients also vary with regard to their frontotemporal lobar impairment. A proportion meet primary and supporting Neary criteria for FTLD, others have mild or moderate levels of frontal lobe-based behavioral changes, while still others appear normal. Few studies have systematically measured the neurobehavioral changes in an unselected sample of ALS patients, but our lab has conducted structured interviews with caregivers, using the Neuropsychiatric Inventory (NPI).[12] Among a cohort of 24 confirmed ALS patients, caregivers reported a range of mild to moderate symptoms of irritability, disinhibition, depression, apathy and agitation (in that order) as the most common non-motor neuron disease-related complaints seen by ALS caregivers.

THE CONTINUUM OF EXTRAMOTOR CEREBRAL ANOMALY IN ALS

Imaging studies provide support for the neural mechanisms for these cognitive and behavioral abnormalities, documenting cerebral abnormalities that extend well beyond the primary, secondary and sensorimotor cortices. Structural imaging, PET, functional MRI (fMRI) and SPECT data reveal a pattern of rather widespread cortical involvement in ALS, with a worsening of this pattern seen in cognitively or behaviorally abnormal ALS patients. Mild to moderate cerebral atrophy has been documented in ALS patients with unknown cognitive status, with 50% of the sample having parietal atrophy, 38% insula atrophy, 32% frontal, 20% temporal, and 12% occipital atrophy. In addition, white matter degeneration has also been identified, suggesting a loss of fibers from the temporal and parietal lobes. Our group's investigation using voxel-based morphometry identified left middle and inferior frontal gyri, the anterior portion of the superior frontal gyri, the superior temporal gyri, the temporal poles and left posterior thalamus as areas of brain atrophy among ALS patients, with

those patients with comorbid FTLD having more severe frontal atrophy.[13]

ALS patients without frank FTLD have pronounced reductions in regional cerebral blood flow (rCBF) in frontal and anterior temporal cortices on PET, and ALS patients with decreased verbal fluency scores have impaired activation of the dorsolateral prefrontal cortex, premotor cortex, bilateral insular cortex, and thalamus as compared with ALS patients who perform well on fluency measures. ALS patients with diagnosed dementia have decreased uptake in the frontal lobe and some have additional abnormalities in temporal, parietal and right thalamic regions on PET. fMRI data reveal that when nondemented ALS patients perform a verbal fluency task, they exhibit reduced activation in the middle and inferior frontal gyri and anterior cingulate gyrus, in addition to regions of the parietal and temporal lobes.[14] Investigations using SPECT reveal that patients without significant dementia signs have metabolic reduction in the frontal lobe, and those with neuropsychologic dysfunction have abnormal anterior cingulate metabolism and frontal hypoperfusion.

As neuroimaging is a sensitive way to understand anatomically the regions affected in ALS, our group has studied whether cognitively and behaviorally abnormal ALS patients had similar patterns of atrophy to cognitively and behaviorally intact ALS patients, and particularly if ALS patients with sub-threshold signs of dementia demonstrated subclinical disease on MRI. We evaluated 20 non-neurologic controls and 22 consecutive patients presenting to the ALS Center at UCSF, using neuroimaging to assess lobar atrophy and neuropsychological and neurobehavioral interviews to determine cognitive and behavioral functioning. MRI scans were obtained with whole-brain coverage. The scans included 3-dimensional T1-weighted volumes and we used SIENAX software to estimate segmented gray and white matter volumes and transformations to standard templates to segment individual lobar regions.

Lobar gray matter volumes were determined for right and left hemisphere frontal, temporal, parietal, occipital, limbic, and insular regions. We found that the ALS patients with comorbid behavioral or cognitive abnormalities possessed significant reductions in gray matter volume across 11 of the 12 regions of interest (ROIs). Perhaps more striking was the finding that the 11 patients with either full-blown dementia or sub-threshold abnormalities in cognition or behavior also had significant reductions in gray matter in the right frontal, right parietal, and right limbic lobes, as compared with the 11 ALS patients without abnormalities. This anatomic distinction between the two ALS groups suggests that right hemisphere atrophy among ALS patients may represent a biomarker associated with behavioral and cognitive abnormalities. Such right hemisphere deficits have been linked to inappropriate range and intensity of affect and impaired ability to perceive facial expression and voice quality in others. Patients with right hemisphere deficits also have been described as having an 'indifference reaction', tending to deny or make light of the extent of their disabilities. As a result, right hemisphere patients tend to set unrealistic goals for themselves, fail to take limitations into account, and appear unconcerned about their problems – common traits described by family members of ALS patients with behavioral disturbance.

Regarding our hypothesis that atrophy would be identifiable among ALS patients with sub-threshold dementia characteristics, we observed atrophy in patients with executive function deficits yet normal behavior, and even in patients who were normal at baseline evaluation, but who went on to develop executive function problems 1 year later. Although this study employed a small number of subjects ($n = 24$) and the results should be interpreted cautiously, comparisons of individual subjects illustrate a continuum of frontal lobe impairment that mirrors the spectrum of cognitive and behavioral impairment on testing.

Figure 5.1 demonstrates the cerebral atrophy differences in five patients in our study. The right frontal lobe, a region shown to be correlated with cognitive and behavioral deficits, was found to have associated atrophy in each of five subjects illustrated here. The FTLD patient (e) was diagnosed with the frontal variant of FTLD as defined by Neary criteria, with significant disinhibition as measured by the NPI. Included

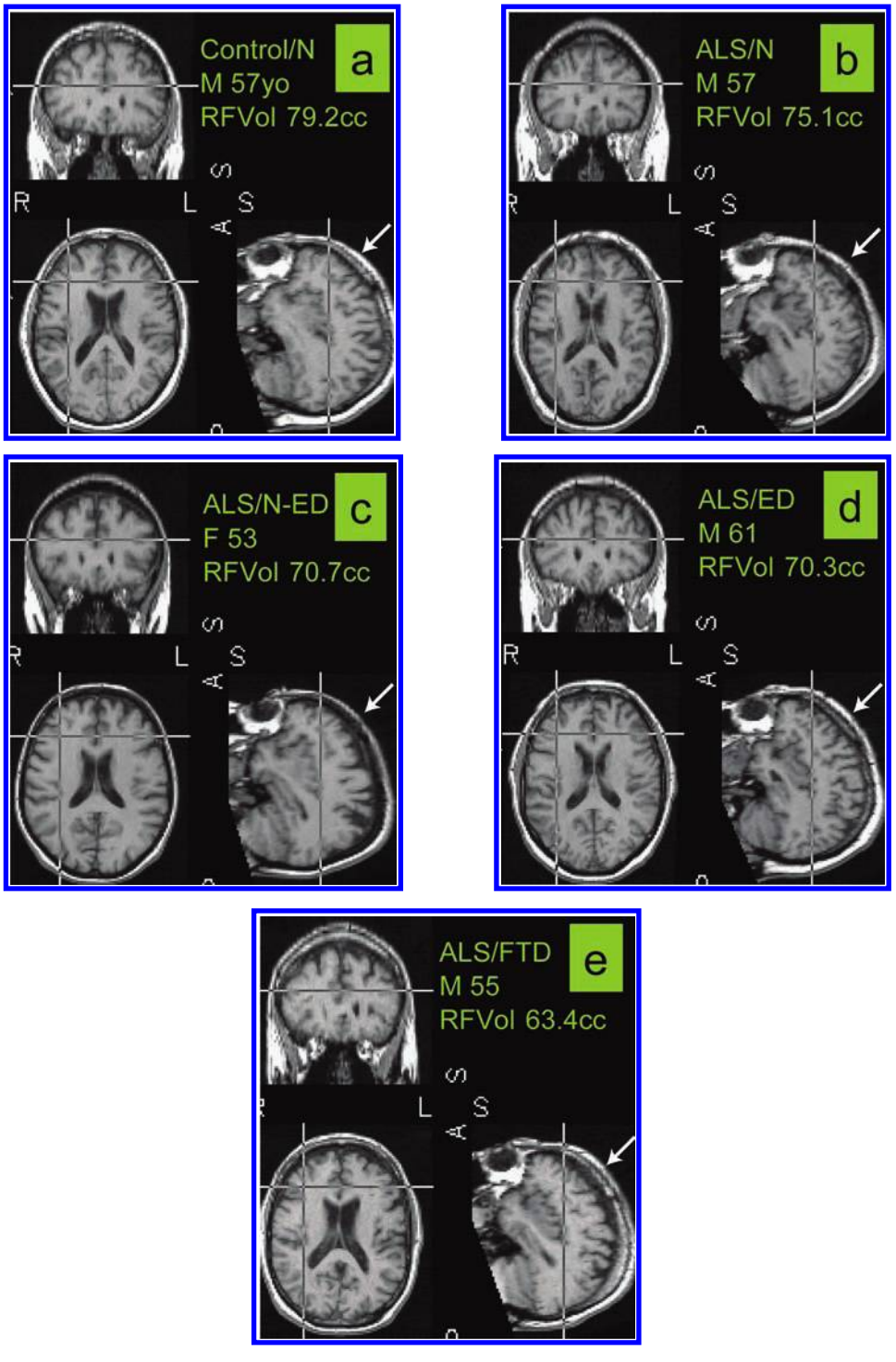

Fig. 5.1 Coronal, axial, and sagittal views of (a) a 57-year-old male normal control, (b) a 57-year-old male ALS patient tested cognitively and behaviorally normal, (c) a 53-year-old female ALS patient tested normal at baseline but ALSci at 1-year follow-up, (d) a 61-year-old male ALSci patient with bilateral frontal atrophy, and (e) a 55-year-old male ALS-FTLD patient with severe bilateral frontal atrophy. Vertical and horizontal lines represent the slice of the brain in which the image was taken, with corresponding views from facing the front of the brain, from above, and from the side.

is a patient (c) with normal cognition and normal verbal fluency at the time of baseline MRI who had reduced gray matter lobar volumes similar to those patients with low verbal fluency score and executive dysfunction. At 1-year follow-up this patient had a dramatic decline in her verbal fluency score, suggesting that her pattern of frontal lobe atrophy preceded her executive dysfunction and could be thought of as a type of biomarker.

SUBTYPING THE SPECTRUM OF FRONTOTEMPORAL CHANGE IN ALS

Our group has suggested that explicit distinctions can be made between subgroups of abnormal ALS patients to more accurately characterize the frequency and nature of cognitive and behavioral abnormalities among ALS patients. The imaging data described above suggest that patients with sub-threshold cognitive and behavioral abnormalities have corresponding cerebral atrophy, indicating that nondemented ALS patients with abnormalities have more than simple hypoxia, depression, or fatigue-related problems. By attempting to group patients into unique subtypes we may advance the field by distinguishing between different etiologies.

A helpful nomenclature may be 'ALS with cognitive impairment' (ALSci) for those ALS patients who perform 1.5 standard deviations (SD) below the mean on at least two executive function neuropsychological measures. A recent review[15] offers the term 'behaviorally impaired' (ALSbi) to describe ALS patients who display frontal lobe-based behavioral signs who do not meet full criteria for FTD. The NPI or other behavioral interviews provide a structure for asking caregivers to rate specific frontal lobe-based behavior changes. Table 5.1 (partially adapted from Lomen-Hoerth and Strong[15]) illustrates specific criteria to distinguish between ALSci, ALSbi, and ALS-FTD.

Table 5.1 Criteria for distinguishing between ALSci, ALSbi, and ALS-FTD

Terminology	*Clinical characteristics*
ALS	A pure motor system disorder as defined by the El Escorial criteria; no clinical evidence of frontotemporal dysfunction
ALSci	Deficits (1.5 SD below the age-matched mean) on two or more neuropsychological tests of executive functioning, but insufficient to meet the Neary criteria for FTD
ALSbi	Frontal lobe-type behavioral impairment in two or more areas, as measured by a standardized caregiver interview
ALS-FTD	ALS patient meeting Neary criteria for FTD

ALSci, ALS with cognitive impairment; ALSbi, ALS with behavioral impairment; FTD, frontotemporal dementia.

CONSENSUS BUILDING TOWARDS A STANDARDIZED NEUROPSYCHOLOGICAL ASSESSMENT BATTERY

Investigators in the fields of FTLD and ALS came together to discuss the considerable progress made in characterizing these overlapping syndromes in a consensus conference in March 2005. Neuropsychologists representing many laboratories discussed the utility of standardized tools of measurement. Areas of agreement included the utility of a standardized battery that could be compared across laboratories, and the identification of important clinical variables to control for when identifying ALS patients with cognitive and behavioral impairment. Depression, pseudobulbar affect, hypoxia, forced vital capacity status, educational level/baseline intellectual functioning, presence of bulbar palsy, and level of disease progression are important clinical variables to control for when studying ALS patients. Neuropsychologists in the field also agreed that an acceptable neuropsychological battery should be weighted towards tests of executive function, including at least one measure of verbal fluency. Also included in the battery should be at least one caregiver interview that measures frontal lobe behavior. Finally, the gold standard of identifying full-blown FTLD should employ the Neary criteria. While this working group was not an official body charged with representing all labs' perspectives, it was a first step in what is hoped

will be a more collaborative process, where clinicians in this field share resources to advance our understanding of the identification and measurement of cognitive and behavioral changes in ALS.

Another area of agreement involved the need for the development of a brief screening battery to identify ALS patients with cognitive and behavioral abnormalities. While it was agreed that a full neuropsychological assessment was required as the gold standard for proper diagnosis of FTLD, many small clinics do not yet have a neuropsychologist on staff. With an abbreviated screening battery, nursing staff or research assistants may identify patients with cognitive and behavioral abnormalities and then refer them to an affiliated neuropsychologist for a conclusive evaluation. Such a screening battery would likely involve a verbal fluency measure and a caregiver questionnaire focusing on behavioral changes.

CLINICAL SIGNIFICANCE OF FRONTOTEMPORAL CHANGES IN ALS

The clinical significance of comorbid FTLD and ALS, or ALS with milder forms of frontotemporal changes, is not yet well understood. A retrospective cohort study was undertaken by our group to test two clinical impressions that our group has developed since we have started to recognize the executive and behavioral dysfunctions that characterize FTLD as a common feature among our patients with ALS.[10]

We hypothesized that patients with ALS-FTLD would be less compliant with recommended treatments and have a shorter survival than those with ALS who have normal executive and behavioral function. Of 100 ALS patients examined, 28 were identified as having either full-blown FTLD or a milder variant of cognitive or behavioral disturbance. Of this group, the median survival from symptom onset of ALS was 2 years 4 months for the 28 patients with frontotemporal abnormalities and 3 years 3 months for the 53 ALS patients without cognitive changes (not including a group of patients with ambiguous cognitive status). Relative hazard indices indicated that the presence of frontotemporal changes predicted shorter survival among ALS patients, as did older age (>59 years at onset) and the presence of bulbar onset ALS. The presence of both bulbar onset ALS and frontotemporal abnormalities signaled a syndrome where lifespan is shortened (Fig. 5.2).

Given the study design, we cannot make assumptions about the mechanism of the shortened survival rate. The noncompliance data do suggest, however, that patients with frontotemporal abnormalities were at greater risk for noncompliance. Noncompliance with noninvasive positive-pressure ventilation (NPPV) was 75% in ALS patients with frontotemporal abnormalities vs 38% in ALS without frontotemporal abnormalities (relative risk for noncompliance 2.00, CI 1.1 to 3.6; $p = 0.013$). Noncompliance with percutaneous endoscopic gastrostomy (PEG) was 72% in ALS patients with frontotemporal abnormalities vs 31% in ALS without frontotemporal abnormalities (relative risk 2.34, CI 1.0 to 5.6; $p = 0.022$). The association between frontotemporal abnormalities and noncompliance with either NPPV or PEG persisted even after controlling for age.[10]

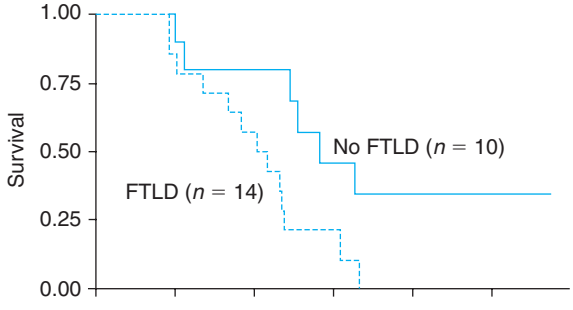

Fig. 5.2 Kaplan–Meier survival estimates for 24 patients with ALS with bulbar onset of disease by presence or absence of frontotemporal lobe dementia (FTLD). Log-rank test for equality of survival functions, $p = 0.038$.

ONGOING DEBATES IN THE FIELD

Perhaps most hotly debated is the question of the true prevalence rate of ALS patients with comorbid FTLD. This question is most likely fueled by referral bias, with some investigators studying all ALS patients in a given clinic and

other labs studying selected patients referred from other clinics. Complicating this issue is the fact that the rapid progression of the motor neuron disease out-paces the FTLD syndrome, frequently resulting in patient death before the frontotemporal neuron loss becomes clinically apparent.

The utility of subtyping patients into distinct categories of cognitive and behavioral impairment (lumpers vs splitters) has become a second, closely related debate. Patients with mild or moderate cognitive and behavioral deficits can either be subdivided into distinct categories or instead lumped into the category of 'non-demented'. Our group maintains that by carefully measuring behavioral impairment and cognitive functioning on a continuum, using sensitive measures that identify mild to moderate cognitive and behavioral changes, distinctions can be made between patients who have only one area of pathology, and others who share both. Our investigations suggest that the ALSci patients do not display behavioral abnormalities consistent with FTLD. Yet other patients categorized as ALSbi did not meet criteria for significant cognitive impairment, nor did they meet Neary criteria for a full-blown dementia syndrome. By distinguishing these two groups from those patients traditionally characterized as ALS-FTD, investigators may uncover unique pathological mechanisms and different trajectories of clinical course.

CONCLUSIONS

The concept that cognitive and behavioral dysfunction in ALS is rare can no longer be substantiated. Critical questions now include the prevalence of the dysfunction and the possible etiologic differences between those ALS patients who are cognitively and behaviorally normal and those with abnormalities. ALS may exist as a degenerative process of the motor system, in which degeneration of the frontotemporal lobar type can occur. When prominent, these changes may manifest as frontotemporal lobar degeneration (ALS-FTLD). In its more subtle manifestations, either a frontal dysexecutive syndrome or behavioral syndrome may occur, or both. It is intriguing, however, that frontal, temporal and parietal cortical atrophy, observed on neuroimaging, and disproportionate to that observed in age-matched controls, is seen across all ALS patients. These data support the concept that a 'pure' phenotype of ALS in which the disease process is restricted to the motor neurons is in fact rare, and that the more common variant is a more complicated phenotype in which the neurodegeneration extends well outside the boundaries of the motor system.[16,17]

Consensus terminology is required to bring some order to what is becoming an increasingly complex picture. Additionally, investigators are encouraged to use thorough neuropsychological batteries, appropriate neurobehavioral measures and clear, well-defined categories of cognitive status to advance the field. One prospective study has observed that over the course of 12 months, nondemented patients do not go on to develop FTLD.[18] More prospective studies are required to answer such questions about the clinical trajectory and clinical impact of cognitive and behavioral changes among ALS patients.

ACKNOWLEDGMENTS

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6

The spectrum of altered cognition in amyotrophic lateral sclerosis

Stanley H Appel, George M Ringholz and Paul E Schulz

COGNITIVE DYSFUNCTION IN SPORADIC ALS

Recent studies suggest that the clinical and pathological expression of amyotrophic lateral sclerosis (ALS) extends beyond the involvement of upper and lower motor neurons to include cognitive dysfunction and frontal temporal pathology. In 1996, we reported on 146 patients with typical, sporadic (nonfamilial) ALS,[1] 36% of whom displayed evidence of clinically significant impairment, performing at or below the fifth percentile on at least two of eight neuropsychological measures compared with relevant normative data. Deficits were most common in the areas of problem-solving, attention/mental control, continuous visual recognition memory, word generation, and verbal free recall. Dysarthria, low education, and greater severity of motor symptoms were risk factors for impairment.

Other studies similarly document compromise of frontal executive dysfunction with impairment of attention, working memory, and verbal fluency in patients with ALS.[2–9] Collectively these reports suggest an overlap or a continuum between ALS and frontotemporal dementia (FTD). This overlap was also reported in a study of patients with frontotemporal dementia with no known diagnosis of ALS or family history of ALS. Of 36 patients evaluated, 5 met criteria for definite ALS and an additional 13 met criteria for possible ALS.[10]

Our more recent report of cognitive function in ALS represents the largest group of ALS patients yet studied.[11] We examined a new group of 316 consecutive patients; 28 were excluded because of having familial ALS. Nine were excluded because of a history of neurological conditions affecting cognition, such as stroke, traumatic brain injury, major depression, psychosis, or Alzheimer's disease. There were 279 remaining patients with probable or definite sporadic ALS (sALS) by El Escorial criteria. These patients with sALS were compared to 129 control subjects selected with the same exclusion criteria. We employed four methods to assess and compare cognition across groups: Mini-Mental Status Exam (MMSE) scores, neuropsychological testing cut-off scores,[11] cluster analysis, and clinical evaluation employing the patient interview and exam, family interview, and cognitive testing.

The ALS patients matched our overall database population of patients.[12] Mean age was 59 (SD = 14.1) years and the median time from symptom onset to first clinic visit was 16.3 (SD = 12.3) months. In all, 61% of the patients were male, and the mean education level was

13.6 years. In 66% of the patients, onset of disease was in the limbs, while 34% of patients had bulbar onset. The mean score of these patients on our Appel ALS (AALS) rating scale was 68. This score indicated that the patients had mild impairment of extremity strength and function, as well as speech, swallowing, and respiratory function. Scores on the Geriatric Depression Scale averaged 7.8, indicating the absence of significant depression. The control population of patients were comparable, except for being slightly older (74.4 years, SD = 6.3) and slightly more educated (15.6 years, SD = 2.2), thereby necessitating normalization of test scores for age and education.

By computerized cluster analysis, the cognitive performances of the ALS patients were readily divisible into intact (49%), mild (32%), and moderately to severely impaired (19%) performances. Only 5% of the control group fell into the mildly impaired range and 95% were intact (Table 6.1). These data probably underestimated the number of affected sALS patients because behavioral changes were not included. Moreover, timed tests and tests utilizing the motor systems were excluded, thereby reducing the number of parameters compared across groups.

As demonstrated in Fig. 6.1, patients with ALS scored more poorly on tests of attention/concentration (the Verbal Series Attention Test) as well as tests of memory (Logical Memory I subtest – immediate recall, Logical Memory II subtest – delayed recall, Visual Reproduction I subtest – immediate recall, Visual Reproduction II – delayed recall). Benton Facial Recognition Test (BFRT) and MMSE scores (not shown) were similar between controls and ALS patients, except for severely impaired patients. The American version of the National Adult Reading Test (AMNARQ), an estimate of premorbid verbal IQ, was also similar in control and ALS populations, except for severely impaired ALS patients.

The distribution of ALS patients into intact, mild, and moderate/severely impaired categories by cluster analysis was essentially similar to assessments utilizing MMSE scores, cut-off scores,

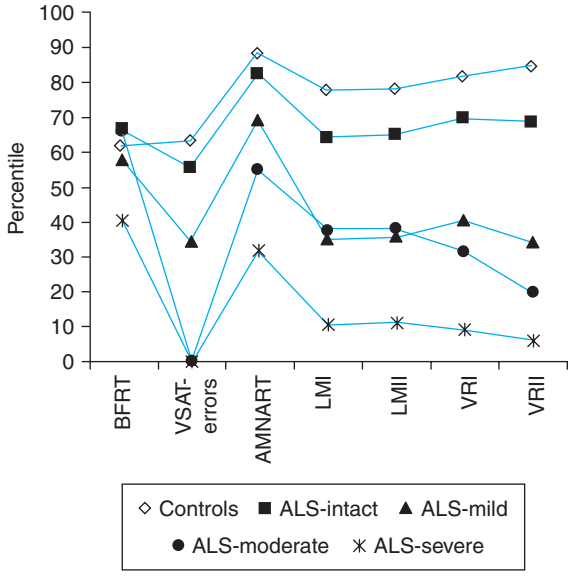

Fig. 6.1 Comparison of cognitive performance in normal controls vs four amyotrophic lateral sclerosis (ALS) groups. BFRT, Benton Facial Recognition Test; VSAT, Verbal Series Attention Test; AMNART, American National Reading Test; LMI, Logical Memory subtest from the Wechsler Memory Scale-Revised (immediate recall); LMII, Logical Memory subtest from the Wechsler Memory Scale-Revised (delayed recall); VRI, Visual Reproduction subtest from the Wechsler Memory Scale-Revised (immediate recall); VRII, Visual Reproduction subtest from the Wechsler Memory Scale-Revised (delayed recall). Reprinted with permission from: Ringholz GM, Appel SH, Bradshaw M, et al. Prevalence and patterns of cognitive impairment in sporadic ALS. Neurology 2005; 65:586–90.

Table 6.1 Distribution of control and ALS patients by cluster

Cluster group	*Intact*	*Mild*	*Moderate*	*Severe*	*Total*
Control	122 (94.6%)	7 (5.4%)	0	0	129
ALS	136 (48.7%)	90 (32.3%)	36 (12.9%)	17 (6.1%)	279

and clinical diagnoses (Table 6.2). MMSE scores were divided into those over 27, 25–27, and below 25. Cut-off scores were based on neuropsychologic test results: mild impairment was defined as performance below the fifth percentile on two or more measures, and moderate to severe impairment was defined as performance more than two standard deviations (SD) below the mean on three or more measures. Clinical diagnoses were determined based on a comprehensive history and physical examination, discussions with the patient's family, and neuropsychologic testing.

Overall, approximately 50% of patients had some degree of cognitive impairment. In 30% of patients, the impairment was mild with no clinical evidence of dementia, while in 20% the impairment was moderate to severe. The alterations were primarily in executive function, especially attention, concentration, and working memory. Of the 43 patients with a clinical diagnosis of moderate/severe impairment, 41 met criteria for FTD: 15 with behavioral onset and 26 with language onset. Two patients had severe memory loss and deficits in multiple other cognitive domains, and were diagnosed as probable AD.

Our present data do not suggest that these diverse patterns represent discrete subtypes. Sporadic ALS is recognized as being clinically heterogeneous with variation in site of onset, rates of progression, and rates of survival.[12] The patterns of cognitive dysfunction in ALS patients may similarly represent heterogeneity in the range and extent of executive, language, and behavioral dysfunction. With respect to the executive dysfunction noted in mildly and moderately impaired ALS patients, similarity in the patterns of cognitive performance is more suggestive of differing levels of severity or stages of a progressive disease. The hypothesis of a continuum is also supported by the pathological demonstration of tau-positive inclusions in the frontal cortex of patients with sALS, especially the greater presence of inclusions in patients with cognitive impairment.[13]

In a recent MRI voxel-based morphometry study of patients with ALS with and without clinically evident frontotemporal lobar dementia (FTLD), a common pattern of gray matter atrophy was reported in frontotemporal regions.[14] Most of the frontal regions appeared to be more atrophied in the ALS/FTLD group than in the ALS group. This report is in accord with a continuum between ALS and FTLD.[15–17] Such studies collectively suggest that frontal atrophy may be present in patients without clinically evident FTLD. They also support the concept of a clinical and anatomic continuum between ALS and frontotemporal degeneration.

The key question is whether cognitively and behaviorally normal ALS patients develop neuropsychological evidence of frontotemporal dysfunction prior to motor neuron injury or subsequent to disease progression. A recent study of 20 ALS patients at a 6-month interval documented that patients with ALS became slower over this 6-month time period on a test

Table 6.2 Percentage of patients in each cognitive category vs type of analysis

	Cognitive category					
	Intact		*Mild*		*Moderate and severe*	
Type of analysis	*n*	*%*	*n*	*%*	*n*	*%*
MMSE	129	48.9	85	32.2	50	18.9
Cluster analysis	136	48.8	90	32.3	53	19.0
Cut-off scores	136	48.7	107	38.5	36	12.9
Clinical diagnosis	147	52.9	89	31.9	43	15.4

of simple word retrieval.[7] However, impaired written and spoken verbal fluency as well as emotional lability in ALS patients did not deteriorate over the 6-month time period. It is still unclear whether impairment of verbal fluency is an early manifestation of sALS. Furthermore, is impaired verbal fluency present before or at early stages of muscle weakness and motor neuron injury in sALS?

Perhaps the anecdotal concept of ALS as a 'nice guys' disease provides a clue as to when frontal impairment begins. When queried, family members often report that the patient with sALS 'has always been a nice guy.' If the 'nice guy' persona relates to frontal function, then frontal changes may precede or, at the very least, occur concomitantly with motor neuron injury. Furthermore, this concept, if validated by careful study, might suggest that in sALS the behavioral and personality changes may precede the motor deficits by a substantial period of time.

Clearly, detailed neuropsychological and structural studies of ALS patients in the earliest stages of motor weakness are needed. Furthermore, extensive prospective longitudinal studies of sALS patients, including neuroimaging and neuropsychological investigations, would extend our understanding of the natural history of ALS and its relationship to frontotemporal degeneration.

COGNITIVE DYSFUNCTION IN FAMILIAL ALS

We recently initiated a study to determine whether cognitive impairment was compromised in patients with familial ALS (fALS) (Schulz et al., unpublished data). To be categorized as fALS, at least one first-degree relative with ALS was required. In our preliminary analysis, 37 patients with familial ALS were studied with the same techniques used to evaluate sporadic ALS. Unfortunately, genetic testing is not yet available for these fALS patients, and it is not known whether these patients have SOD1 mutations or are linked to FTD/ALS on chromosome 9 or 17. In the fALS patients, cognitive impairment was present to the same extent, or possibly to a slightly greater extent, than we noted in patients with sALS. The pattern of impairment in fALS patients was also similar to the pattern in sALS patients: namely, compromise of executive dysfunction characterized by impaired attention, concentration, and verbal fluency. Furthermore the percentage of fALS patients with executive dysfunction was slightly greater than the 50% noted in sALS patients. What was most intriguing was the relatively similar cognitive impairment in our patients with fALS despite the likely heterogeneity of genetic defects. Thus despite the heterogeneity of clinical courses in patients with sALS and the different genetic defects in patients with fALS, executive dysfunction may well be a common pattern of cognitive compromise.

It is of considerable interest that whether evidence for cognitive dysfunction precedes or follows evidence of motor neuron dysfunction in fALS is usually a function of whether the patient was seen first in a dementia clinic or an ALS clinic. As noted with sporadic disease, FTD may precede ALS, or ALS may precede FTD. In one of our recent cases of fALS, a 48-year-old male, with a father and several uncles with documented ALS, presented with a 2-month history of weakness in the right hand. The presence of weakness in two limbs, hyperreflexia in all limbs, a positive jaw jerk, and EMG evidence of motor neuron disease in arms, legs, and thoracic paraspinous musculature confirmed the diagnosis of ALS. By detailed neuropsychological testing, he met the criteria for FTD including significantly impaired verbal fluency. Of greatest interest was the statement by his sister, confirmed by his mother, that approximately 3 months prior to the onset of weakness the patient became much 'quieter'; and his relationship to his family and friends changed. He had been a brilliant, hard-driving, aggressive former marine and police officer, and had now become a placid 'nice guy.' He would often repeat some of his thoughts. Similar anecdotal experience from other patients with fALS suggests that frontal cognitive changes may precede the manifestations of motor neuron injury. However, this point needs detailed validation. As noted in our own study, there were patients with fALS in whom motor manifestations were present at a time when detailed neuropsychological evaluations documented no

evidence of frontal dysfunction. However, we do not know whether such patients had any evidence of structural changes in a frontal-temporal distribution, or evidence of pathological alterations.[18]

If frontal and motor dysfunctions are manifestations of a continuum of disease, one would anticipate that patients may present with either. It would then be important to clarify whether the initial motor or frontal manifestations of fALS depend upon the specific gene or mutation involved. Only by detailed neuroimaging combined with detailed neuropsychological testing at varying stages of disease from the earliest stages of disease will we be able to define the temporal patterns of frontal and motor neuron dysfunction in both sALS and fALS.

ACKNOWLEDGMENTS

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7

The spectrum of cognitive dysfunction in ALS/MND in the Japanese population

Makoto Tanaka and Koichi Okamoto

INTRODUCTION

The symptoms of classical amyotrophic lateral sclerosis (ALS), which are confined to the voluntary motor system with varying degrees of upper and lower motor neuron involvement, do not include memory, intellectual, behavioral and psychiatric derangement. Dementia associated with ALS and usually with parkinsonism is known in small populations in the Western Pacific.[1] This type of association of cognitive and motor symptoms has been studied intensively and established as a disease entity. Reports of another type of dementia with ALS have come mainly from the Japanese population,[2,3] and led to recognition of patients in the European and North American populations,[4,5] bearing a close resemblance to the Japanese patients.

In Japan, since the first report[2] of the patient with ALS and dementia characterized by his peculiar behavioral and psychiatric symptoms in 1964, many patients with similar symptoms have been reported. This kind of cognitive dysfunction associated with ALS was clinically and pathologically recognized as a subtype of frontotemporal dementia (FTD) in Japan as well as in Western countries.

The purpose of this chapter is to provide a clinical overview of FTD in the Japanese ALS population against a backdrop of the rich history of describing this entity in the Japanese literature, and to understand whether this is a distinctive entity compared to that in the European and North American populations.

THE FIRST CASE REPORT OF ALS WITH DEMENTIA IN JAPAN

Dr Ryouji Yuasa[2] described a patient with both typical neurological features like motor neuron disease and typical behavioral and psychiatric symptoms like FTD. The case report illustrating a perfect type of ALS with dementia has been respected in Japan. Unfortunately, this report was written in Japanese and only an English abstract was available. The abstract is given with minimal modification below.

> A 47-year-old man was first admitted to Dr Yuasa's hospital on August 22, 1963, because of mental changes over a period of 8 months. Family history was negative. His mental changes were characterized by behavioral and personality changes as well as disturbances in memory, calculation and judgment. For example, he became neglectful of personal appearance. He bought something for his children day after day on his way home from the office. He appeared indifferent to his inability and cognitive

dysfunction. On admission, he was apathetic and stereotypic behaviors were noted. He washed his ashtray every 10 minutes. Disinhibited behaviors were also obvious. He wandered about aimlessly, untidily dressed, and entered other patients' rooms without knocking. Assessment using WAIS yielded a verbal IQ of 66, performance IQ of 69 and full scale IQ of 64.

Muscle atrophy and weakness were evident in the shoulder girdle, arms and hands, and he had lost much weight (Fig. 7.1). Many fasciculations were visible in these atrophied muscles and moreover in the tongue, neck and both thighs. There were positive sucking and snout reflexes, but deep tendon reflexes in the lower extremities were normal. Sensation was intact. Electromyogram showed destruction of anterior horn cells in the spinal cord, and pneumoencephalograms revealed slight dilatation of anterior parts of both lateral ventricles.

He progressively got worse. Muscle atrophy became severe and developed in the face, neck, breast and lower extremities. Six months after admission, difficulty in swallowing, speaking and breathing began to develop. Although knee and ankle jerks increased, no clonus was elicited. He deteriorated more markedly mentally and died of respiratory failure on March 26, 1964. The clinical diagnosis was amyotrophic lateral sclerosis with organic dementia.

Dr Yuasa believed that in this case the dementia resulted from cerebral atrophy, and that the cerebral atrophy and amyotrophic lateral sclerosis should be the expression of one pathologic process.

Fig. 7.1 Photograph of the patient taken on October 10, 1963 showing clearly the distribution of his muscle atrophy. Muscle atrophy and weakness were evident in the shoulder girdle, arms and hand. Reproduced with permission from Yuasa R. Clin Neurol 1964; 4:529–34.

In summary, the patient showed: (1) motor neuron symptoms and signs (MNS) characterized by the involvement of muscles over the shoulder girdle, arms and hands, and much less involvement of the lower extremities (Fig. 7.2); and (2) behavioral and psychiatric symptoms of dementia (BPSD) characterized by apathy, disinhibition and stereotypy, indicating FTD as a term of disorder representing that condition today. Dr Yuasa well recognized that the BPSD of his patient were rather close to those of Pick disease. Furthermore, he suspected that a single disease would express both the MNS and BPSD of his patient. Although his patient was autopsied in a university hospital, the pathologic findings were not reported.

CLINICAL FEATURES IN MND-D IN JAPAN

The patient Dr Yuasa reported has been thought to be typical of motor neuron disease associated with dementia (MND-D) and was followed by many case reports with similar symptoms in Japan. Their average motor and psychiatric symptoms and signs were reported based on the limited number of clinical or pathological cases.[6,7] To understand the ordinary and characteristic symptoms and signs of Japanese MND-D, we conducted literature searches. We have discovered more than 200 cases of MND-D reported in Japan from 1964 to 2004. Among them, we collected reports with information about the age of onset and gender or more, even if they were in an abstract form.

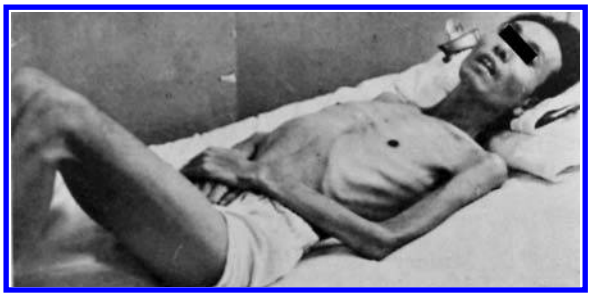

Fig. 7.2 Photograph of the patient taken on March 25, 1964, the day before he died. His legs were relatively preserved, so he was able to walk by himself at the terminal stage. Reproduced with permission from Yuasa R. Clin Neurol 1964; 4:529–34.

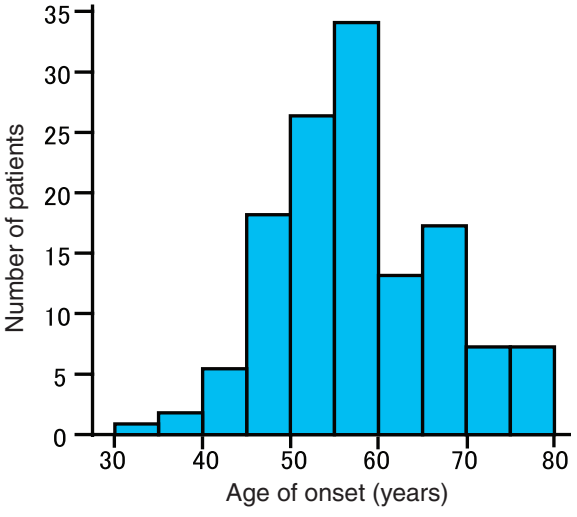

Fig. 7.3 Distribution of the age of onset.

Presenting symptoms and natural course of the disease

As a result of literature searches, a total of 130 cases comprising 70 men and 60 women was analyzed. The mean age of onset was 57 years for all the patients, 56 years for men and 59 years for women (Table 7.1). Ages of onset were distributed from 30 to 78 with a peak in the late fifties (Fig. 7.3).

Presenting symptoms were divided into motor and psychiatric symptoms. Motor symptoms resulting from upper and lower motor neuron involvement included motor weakness, muscle atrophy, fasciculations, spasticity, and gait disturbances. Psychiatric symptoms here indicated dementia and its related symptoms (BPSD) including memory, cognitive, and behavioral impairment. We picked up the description in each of the reports and found three patterns in 118 cases, as shown in Fig. 7.4. In 51% of the cases, psychiatric symptoms preceded motor symptoms. In 35%, motor symptoms appeared first. Psychiatric and motor symptoms began simultaneously in 14% of patients.

The duration of the disease (from onset to death or to a point in time when the patient was placed on a ventilator) was described in 101 patients. The mean for all patients was 33 months. Disease duration of the three groups divided by their presenting symptoms is summarized in Table 7.2. Group P consists of

Table 7.1 Number of cases of MND-D reported in Japan and the age of onset

	Number of cases	*%*	*Age of onset (years)*	
			Mean	*SD*
Total	130	100	57	9
Men	70	54	56	8
Women	60	46	59	10

In total cases, the range was between 30 and 78, and the median was 57.

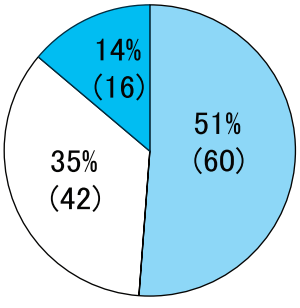

Fig. 7.4 Presenting symptoms in 118 patients with MND-D. Light blue indicates psychiatric symptoms; white, motor symptoms; and dark blue, motor and psychiatric symptoms simultaneously. Figures in parentheses indicate the number of cases with the symptoms.

Table 7.2 Disease duration

Group	Number of cases	Disease duration (months)*	
		Mean	SD
Total	101	33	26
Men	56	31	17
Women	45	36	34
Group P	48	38	31
Group M	30	34	21
Group S	11	23	10

There were cases with disease duration without descriptions of presenting symptoms, therefore, the total number of the three groups (89) was less than the total number (101). Group P, patients presenting with psychiatric symptoms; Group M, patients presenting with motor neuron symptoms; Group S, patients presenting with psychiatric and motor symptoms simultaneously. *Interval from onset to death or the point in time when the patient was placed on a ventilator.

patients starting with psychiatric symptoms; group M, motor neuron symptoms; and group S, both psychiatric and motor symptoms simultaneously. Disease duration was the longest in group P and the shortest in group S. The interval between the onset of motor neuron symptoms and of psychiatric symptoms was calculated. When psychiatric symptoms appeared first, motor neuron symptoms began 19 ± 18 months later (mean ± SD, $n = 47$, max = 168). In contrast, motor neuron symptoms preceded psychiatric symptoms by 11 ± 8 months (mean ± SD, $n = 19$, max = 24) in patients presenting with motor symptoms. Several patients[8] were reported because of a long lag from psychiatric symptoms to motor symptoms. In cases where these exceptional reports were excluded and group S was added to groups P and M, the mean interval from psychiatric to motor neuron symptom onset was 11 ± 16 months ($n = 63$, max = 84), and that in the reverse case was 6 months ± 8 months ($n = 35$, max = 24).

Then, we calculated how long patients with MND-D lived after onset of psychiatric or motor neuron symptoms even if they were not the presenting symptoms. They lived for 23 ± 17 months after motor neuron symptoms began and 32 ± 27 months after psychiatric ones began. Life expectancy in MND-D seems to depend on when motor neuron symptoms start.

In summary, typical MND-D in the Japanese population starts insidiously in the sixth decade of life with BPSP as the presenting symptoms (51%). One or two years later, motor disturbances will overlap the BPSP. In about another 2 years the patient will die or be placed on a ventilator due to the motor neuron involvement. On the other hand, 35% of patients start with MND and in a relatively short period (less than 1 year on average) psychiatric symptoms follow. This type of clinical course seems to be less common in the North American and European populations, as Bak and Hodges[9] stated in their review that cognitive symptoms almost always precede the motor symptoms. However, there are several reports of MND-D[10] showing that the motor symptoms appear first. Dementia is difficult to prove in patients with MND because the motor problems interfere with cognitive evaluation. Moreover, patients with MND-D tend to present first to an MND center rather than a memory disorders center in North America.[11] Because FTD and MND attack different parts of the central nervous system, the specialists caring for the patients have vastly different areas of expertise and interests. There is a study[12] reporting that appropriately applied tests could reveal frontal executive deficits in half of MND patients. These patients would not be diagnosed as having FTD before they pass a certain clinical threshold. In Japan, the rich history of describing MND-D could prompt the specialists to become aware of the presence of dementia in MND patients. This would partially explain why the proportion of patients starting with MND appears to be greater in Japan than in North America or European countries.

Cognitive dysfunction in MND-D

According to the clinical description, we classified the patients into two groups: Alzheimer disease (AD) type and FTD type. Diagnosis of dementia primarily depended on the authors who reported each patient. However, in cases where there was no conclusive diagnosis of dementia, the type was judged from the clinical description of dementia, by considering several criteria proposed previously.[13,14] AD type accounted for only 9 (15%) of 61 patients who

had enough clinical information to determine the diagnosis and most patients were considered to be FTD type (Table 7.3). Even if this classification cannot be strictly defined because of the limitations of the clinical description, it is clearly demonstrated that the nature of cognitive dysfunction in MND-D is far from that of typical AD and is essentially the same as that of FTD.

Severity of dementia was estimated by HDS or HDS-R or Minimental State Examination (MMSE). HDS and HDS-R[15] are simple Japanese tests widely used in Japan and comparable to MMSE in English-speaking countries. These three tests are useful for screening AD and one of them was adopted in many cases we reviewed, whereas they are apparently lacking in evaluating behavioral changes seen in FTD. As we could not find any other semiquantitative measure in common, we used one of them as a rough guide for grading dementia. The score when the diagnosis of MND-D was made or closest to that was analyzed (Table 7.3). Patients were graded according to their score on MMSE or HDS or HDS-R: mild (more than 20), moderate (between 20 and 11) and severe (10 or less). Out of 77 patients who took the test, 17 (22%) were graded as mild, 42 (55%) moderate, and 18 (23%) severe.

FTD includes three subtypes discriminated by major behavioral and psychiatric symptoms:[13] disinhibited, apathetic and stereotypic. Patients in our series were classified into these subtypes according to their cardinal symptoms described. Out of the total 91 patients, 36 (40%) were considered disinhibited, 45 (49%) apathetic, and 10 (11%) stereotypic (Table 7.3). One of these symptoms might appear independently, and more frequently two or more appeared at once or alternately. Therefore, there were some overlapping cases in the figures.

Table 7.3 Classification of dementia in MND-D

Feature	*Number of patients*
Type of dementia	
AD type	9 (15%)
FTD type	52 (85%)
Severity of dementia at diagnosis of MND-D	
Mild	17 (22%)
Moderate	42 (55%)
Severe	18 (23%)
Clinical subtype of FTD	
Disinhibited	40 (36%)
Apathetic	49 (45%)
Stereotypic	10 (11%)

See text for grading of dementia.

Neurological symptoms and signs

Major neurological symptoms and signs observed in the clinical course of our series in the literature are summarized in Table 7.4. Bulbar palsy and muscle weakness and atrophy in the upper extremities or in the shoulder girdle were most common. Obvious bulbar palsy was present in 87% of patients. Muscle weakness and atrophy in the upper extremities or the shoulder girdle were present in 91% of patients. Patients with only fasciculations seen over the muscles are not included. As Dr Yuasa described, muscle weakness and atrophy in the arms and shoulders as well as bulbar palsy were usually severe and tended to appear early in their clinical course. In contrast, muscle weakness and atrophy in the lower extremities or the pelvic girdle were not so common. They were present in only 24% of patients.

Tendon reflexes tended to be hyperactive more in the lower extremities than in the upper extremities. Extensor plantar responses were absent in more than half of the patients. Muscle rigidity as one of the extrapyramidal signs was described in 21% of patients, and was usually mild.

Yoshida[16] reported that in typical MND-D degenerative changes were found in both the lower and upper motor neuron systems and were consistent with classical ALS. However, she also noted that neuronal loss in hypoglossal nuclei and cervical and thoracic anterior horns was severe, in contrast to the relatively mild neuronal loss in the lumbosacral anterior horn. In accordance with the results of the pathological studies, MND-D tends to show the involvement of the tongue, arms and shoulders with the legs being relatively spared. These neurological features have been recognized and

Table 7.4 Summary of neurological symptoms and signs

Symptoms/signs	*Present*	*Absent*		*Total*†
Bulbar palsy	87%	13%		95
Involvement* of the U/E or the shoulder girdle	91%	9%		93
Involvement* of the L/E or the pelvic girdle	24%	76%		92
Tendon reflex	*Hypoactive*	*Normal*	*Hyperactive*	
U/E	17%	38%	45%	73
L/E	11%	33%	56%	73
	Present	*Absent*	*Equivocal*	
Extensor plantar responses	43%	52%	5%	76
Mild muscle rigidity	21%	79%	0%	70

U/E, upper extremities; L/E, lower extremities.
* Muscle atrophy and weakness.
† Total number of patients analyzed.

supposed to be prompts to consider MND-D. However, there are a considerable number of patients with MND-D whose neurological symptoms and signs are indistinguishable from those of classical ALS.[17,18]

Mild muscle rigidity was found in 21% of patients with MND-D. This clinical sign is also comparable to the pathology in the substantia nigra in MND-D. Moderate to severe neuronal loss and gliosis without Lewy bodies are usually found in the substantia nigra.[16] Their frequency (21%), however, appears to be a little too high. It is easy to collect reports of patients with muscle rigidity described, whereas absent muscle rigidity must be infrequently described in patients with normal muscle tone. This would partially explain the relatively high frequency of the sign.

BRAIN IMAGING OF MND-D

The first clinical report of MND-D by Dr Yuasa[2] showed slight dilatation of the anterior parts of both lateral ventricles in pneumoencephalograms, reflecting shrinkage of the anterior parts of the brain. Recent brain imaging techniques including computed tomography (CT) and magnetic resonance imaging (MRI) are very useful to morphologically differentiate MND-D from classical ALS. Most MND-D patients were reported with CT findings after it became available widely in Japan. As shown in Fig. 7.5, CT demonstrates chiefly atrophic changes in the frontal lobe and the anterior and medial temporal lobe and dilatation of the lateral ventricles, especially the anterior and inferior horns of lateral ventricles, frequently occurring secondarily to the brain atrophy. MRI is not only sensitive to the atrophic changes, but also reveals some non-morphological abnormalities in MND-D. As shown in Fig. 7.6, MRI demonstrates mild atrophy over the frontal and temporal cortices. T2-weighted images often recover neuronal degeneration in the motor cortex as low signal intensity areas[19] and axonal degeneration in the pyramidal tract as high signal intensity areas.[20] These signal intensity changes, however, indicate upper motor neuron involvement and are not useful for differentiating MND-D from classical ALS. Based on the authors' experience, the signal intensity changes in the motor cortex and pyramidal tract are less frequent in MND-D than in classical ALS. This is supported by some pathological findings that degeneration in the pyramidal tract is usually milder in MND-D than in classical ALS.[6,7]

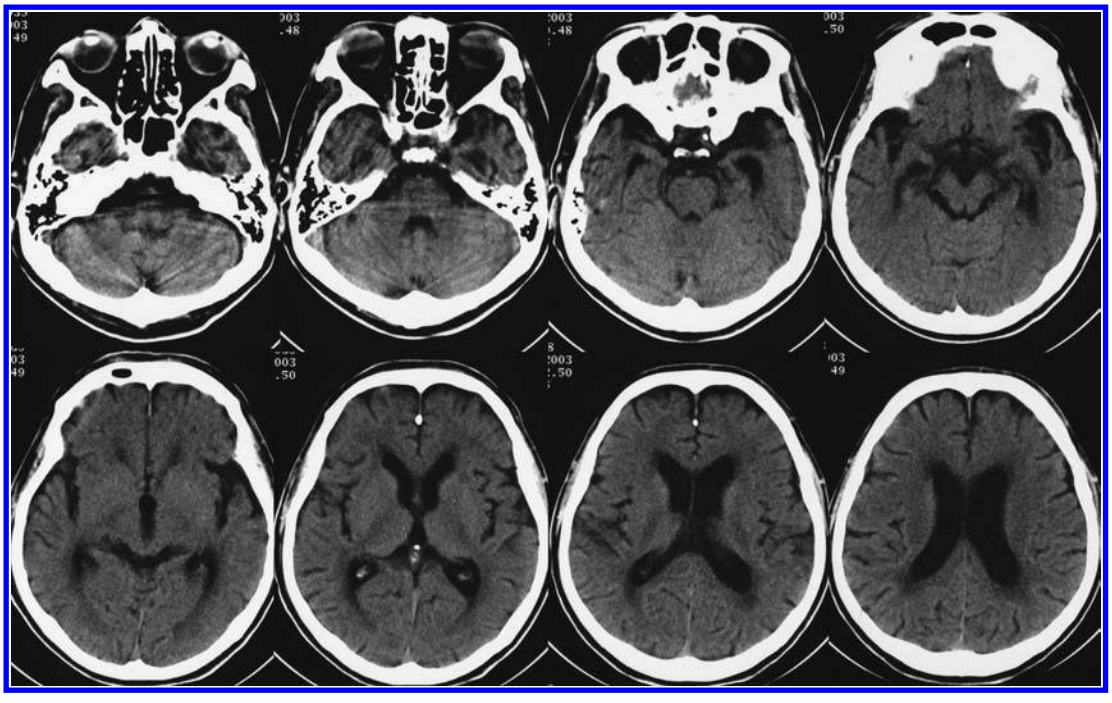

Fig. 7.5 CT of a 69-year-old man with typical MND-D. Atrophy is seen in the frontal and temporal lobes, especially accentuated in the anterior pole and medial structures of the temporal lobes including the hippocampus and amygdala. Images courtesy of Dr Kiyoshi Negoro, Department of Neurology, Yamaguchi University School of Medicine.

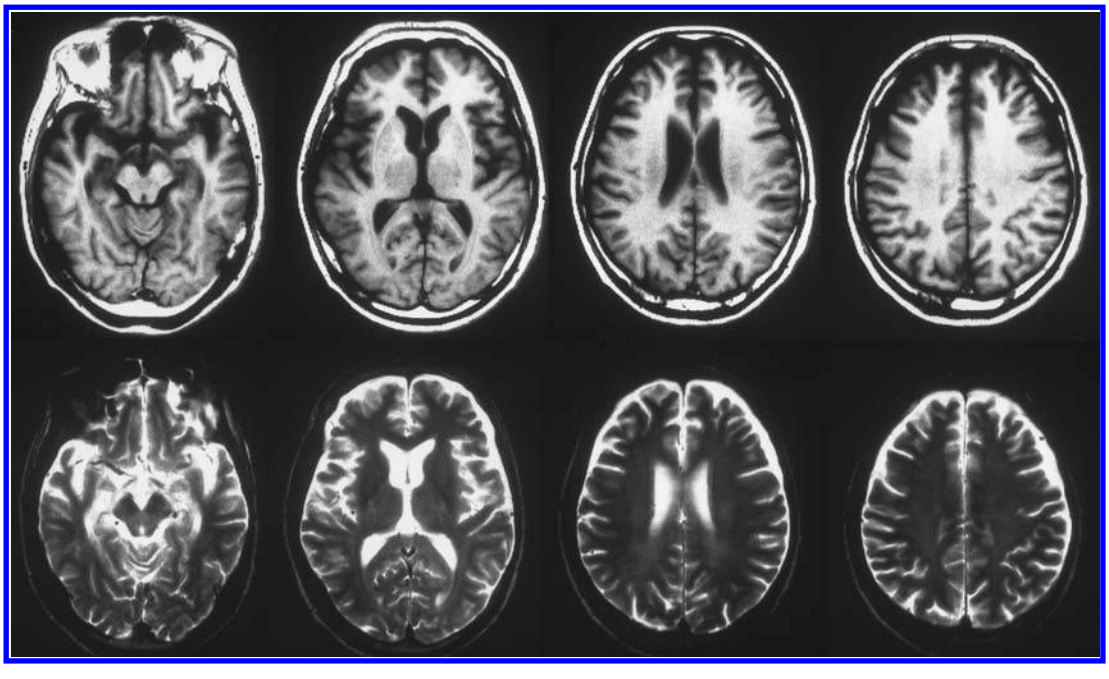

Fig. 7.6 MRI of a 63-year-old man with typical MND-D. Distribution of brain atrophy is essentially the same as the CT of another MND-D patient (Fig. 7.5). There is no abnormal signal intensity in the motor cortex or the pyramidal tract. Top: T1-weighted axial images; bottom: T2-weighted axial images.

In summary, CT and MRI are useful for the diagnosis of FTD in MND, demonstrating brain atrophy in the frontal and temporal cortices. In the Japanese literature, in most clinical cases with MND-D these atrophic changes were assessed by CT or MRI.

Single photon emission CT (SPECT) and positron emission tomography (PET) are more sensitive to the deterioration in the frontal and temporal cortices in MND-D than CT or MRI, since they reflect functional changes in the brain. SPECT is widely available in Japan. In early reports[21] of the cerebral blood flow (CBF) pattern in MND-D, consistent findings were reduced CBF in the frontal and anterior temporal lobes on two-dimensional axial images, with rather poor spatial resolution. Recent studies usually use statistical parametric mapping (SPM) or 3-dimensional stereotactic surface projection (3D-SSP), as shown in Fig. 7.7, allowing us not only to make a diagnosis of FTD in MND more easily but also to investigate the possible relation between the clinical signs and the site of hypoperfusion.

PET is also available to differentiate MND-D from classical ALS. Fluorine-18 labeled 2-fluoro-2-deoxy-D-glucose (FDG) or oxygen-15 gas and oxygen-15 labeled carbon dioxide are usually used as tracers for quantitative PET studies. We studied 10 MND-D patients (Table 7.5), 21 patients with ALS and normal intellectual function (Table 7.6) and 17 healthy controls to see whether decreased CBF and oxygen metabolism would be found in MND-D cerebral cortices outside the primary motor areas, and whether such changes would not be found in ALS without dementia, hoping that these would demonstrate an etiological relationship with the cognitive deterioration in MND-D.[17,18]

Functional images of regional CBF (rCBF) and regional cerebral metabolic rate of oxygen ($rCMRO_2$) in MND-D indicated that cerebral and cerebellar blood flow and oxygen metabolism decreased in all brain regions, especially in frontal regions (Fig. 7.8). Absolute values for rCBF and $rCMRO_2$ in MND-D were reduced in all brain regions examined (Tables 7.7 and 7.8).

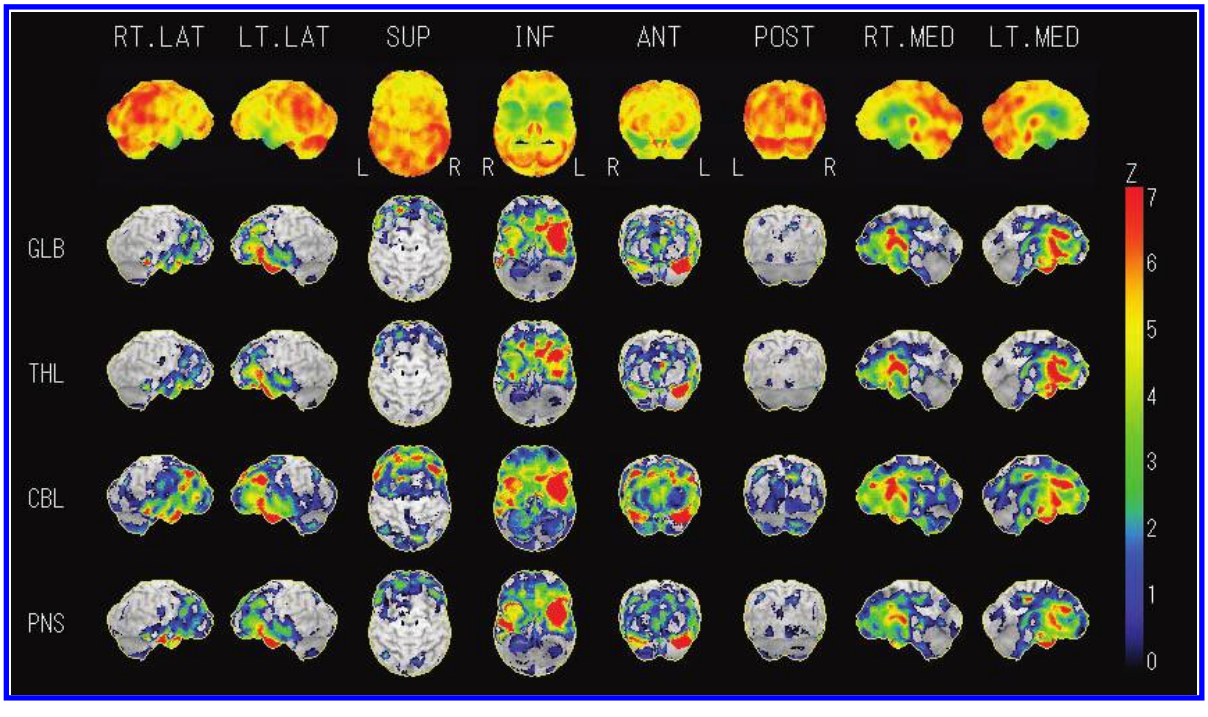

Fig. 7.7 ^{123}I-IMP SPECT with 3D-SSP. CT scans of this patient are shown in Fig. 7.5. Top images indicate 3D-SSP and the color displayed becomes brighter and more reddish with increasing cerebral blood flow. Images courtesy of Dr Kiyoshi Negoro, Department of Neurology, Yamaguchi University School of Medicine.

Table 7.5 Clinical features of MND-D patients

No.	Age	Sex	Disease duration (months)	IQ	VIQ	PIQ	Clinical manifestations									Planar response*	
							Bulbar palsy*	Muscle atrophy†				Tendon reflexes‡					
								L-u/e	R-u/e	L-l/e	R-l/e	L-u/e	R-u/e	L-l/e	R-l/e	L	R
1	52	M	24	<60	<60	63	0	1	1	0	0	1	1	1	1	0	0
2	62	M	8	85	84	90	1	3	3	1	1	1	1	1	1	0	0
3	42	M	8	<60	<60	<60	1	1	1	1	1	3	3	2	2	1	1
4	68	M	11	65	<60	68	1	1	2	1	1	1	1	1	1	1	1
5	75	F	4	67	66	73	1	1	1	1	1	1	1	1	1	1	1
6	50	M	13	69	74	69	1	0	0	0	1	3	2	3	3	1	1
7	57	F	13	95	88	102	0	1	1	0	0	0	0	0	0	0	0
8	64	F	21	79	76	90	1	1	1	0	0	1	1	1	1	1	1
9	61	M	33	52	58	48	1	2	2	0	0	1	1	1	1	0	0
10	60	F	6	52	55	53	0	2	2	0	0	1	1	2	2	1	0

* 0 and 1 indicate absent and present, respectively.
† 0 indicates absent; 1, mild; 2, moderate; and 3, severe.
‡ 0 indicates no response or diminished; 1, normal; 2, hyperactive without clonus; and 3, hyperactive with clonus.
L, left; R, right; u/e, upper extremity; l/e, lower extremity; IQ, intelligence quotient; VIQ, verbal IQ; PIQ, performance IQ.

Table 7.6 Clinical features of ALS patients who underwent the PET study

No.	Age	Sex	Disease duration (months)	Clinical manifestations										Plantar response*	
				Bulbar palsy*	Muscle atrophy†				Tendon reflexes‡						
					L-u/e	R-u/e	L-l/e	R-l/e	L-u/e	R-u/e	L-l/e	R-l/e		L	R
1	69	M	12	1	0	1	0	0	2	3	1	1		1	1
2	47	F	9	0	0	0	0	2	2	2	3	3		0	0
3	39	F	16	1	2	2	1	1	2	2	3	3		1	1
4	60	M	62	1	2	3	1	1	2	1	3	3		0	0
5	49	F	16	0	1	0	1	0	0	2	3	2		0	0
6	58	M	5	0	0	1	0	0	2	3	3	2		0	1
7	67	F	11	0	2	2	1	1	0	0	2	1		1	1
8	55	M	22	0	3	2	0	2	1	2	2	3		0	0
9	64	M	34	1	3	3	1	1	1	1	1	1		1	1
10	68	F	55	0	3	3	3	3	0	0	0	0		0	0
11	68	F	8	0	0	0	1	2	2	2	3	2		1	1
12	68	M	12	1	0	0	0	0	0	0	0	0		0	0
13	45	M	5	0	0	0	0	1	1	1	1	2		0	1
14	39	M	52	1	3	3	2	2	2	2	3	3		1	1
15	71	F	33	1	3	3	2	2	3	3	3	3		1	1
16	41	F	8	0	0	2	0	0	3	3	3	3		0	1
17	51	F	11	0	3	1	0	0	3	3	3	3		1	1
18	53	F	13	1	1	1	0	0	1	1	2	2		1	0
19	59	M	66	0	0	0	1	1	2	2	3	3		1	1
20	45	F	23	1	3	3	1	1	1	1	2	2		0	0
21	65	M	6	1	1	1	0	0	2	2	2	2		0	0

* 0 and 1 indicate absent and present, respectively.
† 0 indicates absent; 1, mild; 2, moderate; and 3, severe.
‡ 0 indicates no response or diminished; 1, normal; 2, hyperactive without clonus; and 3, hyperactive with clonus.
L, left; R, right; u/e, upper extremity; and l/e, lower extremity.

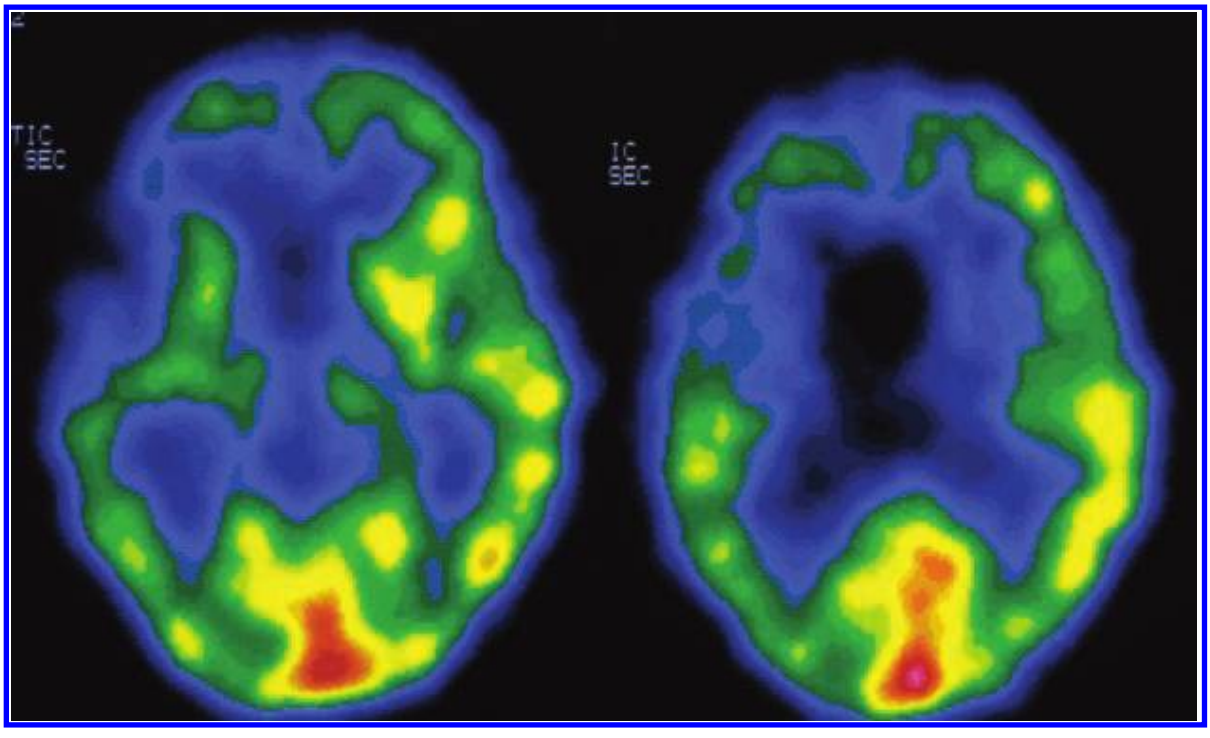

Fig. 7.8 PET images with oxygen-15 gas and oxygen-15 labeled carbon dioxide ($rCMRO_2$). MRI scans of this patient are shown in Fig. 7.6. The varying color differences depend on $rCMRO_2$. Blue indicates low $rCMRO_2$, whereas red indicates high. There is significant reduction of oxygen metabolism in the frontal regions. The temporal regions are also involved predominantly on the left side.

Table 7.7 Regional cerebral blood flow (CBF)

		MND-D (n = *10*)		*ALS* (n = *21*)		*CTRL* (n = *17*)		*ANOVA*	*Post hoc test* p *value*	
Brain area		*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	p *value*	*ALSD vs CTRL*	*ALS vs CTLR*
Frontal cortex	L	25.6	4.2	35.6	4.9	35.9	6.3	< 0.0001	< 0.001	NS
	R	25.9	3.7	36.2	4.9	35.6	6.4	< 0.0001	< 0.01	NS
Temporal cortex	L	28.9	4.0	35.1	5.3	35.9	4.4	< 0.005	< 0.01	NS
	R	29.7	3.6	36.6	4.8	36.3	5.0	< 0.001	< 0.005	NS
Parietal cortex	L	30.5	4.4	36.0	5.3	37.8	5.6	< 0.005	< 0.005	NS
	R	30.8	4.8	36.6	5.4	37.3	6.1	< 0.01	< 0.05	NS
Occipital cortex	L	31.5	4.9	36.7	5.6	37.2	4.6	< 0.05	< 0.05	NS
	R	32.8	4.8	37.8	5.3	38.3	5.6	< 0.05	< 0.05	NS
SMC	L	28.0	4.5	32.4	5.6	38.2	6.2	< 0.0001	< 0.0005	< 0.05
	R	27.2	3.8	33.4	5.1	37.4	6.7	< 0.0001	< 0.0001	< 0.05
mCBF		29.5	3.8	36.3	4.6	36.8	5.1	< 0.0005	< 0.005	NS
Cerebellar hemisphere	L	33.7	7.2	40.8	7.2	39.7	5.1	< 0.05	NS	NS
	R	33.1	5.7	40.0	7.1	38.9	4.6	< 0.05	NS	NS

L and R indicate left and right, respectively. Unit: ml/100 ml of brain tissue/min. Scheffe's F test was used as a post hoc test. CTRL, controls; SMC, sensorimotor cortex; mCBF, mean cerebrocortical blood flow; NS, not significant.

Table 7.8 Regional $CMRO_2$

Brain area		MND-D (n = 10) Mean	MND-D (n = 10) SD	ALS (n = 21) Mean	ALS (n = 21) SD	CTRL (n = 17) Mean	CTRL (n = 17) SD	ANOVA p value	Post hoc test p value ALSD vs CTRL	Post hoc test p value ALS vs CTLR
Frontal cortex	L	2.04	0.30	2.67	0.27	2.92	0.71	< 0.0005	< 0.0005	NS
	R	2.07	0.20	2.67	0.28	2.93	0.78	< 0.0005	< 0.001	NS
Temporal cortex	L	2.46	0.27	2.84	0.42	3.07	0.63	< 0.05	< 0.05	NS
	R	2.51	0.20	2.93	0.36	3.09	0.70	< 0.05	< 0.05	NS
Parietal cortex	L	2.55	0.29	2.83	0.39	3.10	0.56	< 0.05	< 0.05	NS
	R	2.57	0.30	2.90	0.40	3.12	0.59	< 0.05	< 0.05	NS
Occipital cortex	L	2.73	0.46	3.05	0.38	3.22	0.59	< 0.05	< 0.05	NS
	R	2.96	0.37	3.22	0.41	3.48	0.79	NS	–	–
SMC	L	2.31	0.27	2.51	0.44	3.01	0.58	< 0.001	< 0.005	< 0.01
	R	2.29	0.23	2.58	0.42	3.09	0.74	< 0.001	< 0.005	< 0.005
$mCMRO_2$		2.49	0.25	2.89	0.33	3.11	0.65	< 0.01	< 0.01	NS
Cerebellar	L	2.75	0.53	3.02	0.56	3.11	0.56	NS	–	–
hemisphere	R	2.76	0.50	3.04	0.53	3.14	0.61	NS	–	–

L and R indicate left and right, respectively. Unit: ml/100 ml of brain tissue/min. Scheffe's F test was used as a post hoc test. CTRL, controls; SMC, sensorimotor cortex; $mCMRO_2$, mean cerebrocortical oxygen metabolism; NS, not significant.

A significant reduction of rCBF in MND-D was found in all brain regions except for the cerebellar hemispheres. The rCBF and *p* values compared with controls indicated a frontal dominant deterioration of brain perfusion. The $rCMRO_2$ in MND-D also decreased significantly in all cerebral cortices examined except for the right occipital cortex. No significant reduction in $rCMRO_2$ was found in the bilateral cerebellar hemispheres. The frontal areas also seemed the most severely damaged from the viewpoint of $rCMRO_2$. There was no significant relationship between other neurological signs and symptoms and PET data in MND-D.

rCBF and $rCMRO_2$ values in ALS were much higher than those in patients with MND-D. Compared with the controls, a significant difference was found only in bilateral sensorimotor cortices in rCBF and $rCMRO_2$. On visual inspection, there were no distinctive findings in functional images of rCBF and $rCMRO_2$ for this patient group besides the sensorimotor areas. In ALS patients, an exaggeration of some deep tendon reflexes showed a negative correlation with rCBF or $rCMRO_2$ values. Deep tendon reflexes in the left lower extremity correlated with mean cerebrocortical blood flow ($mCMRO_2$, $p < 0.05$) and rCBF in the right frontal cortex ($p < 0.05$). Deep tendon reflexes in the right lower extremity correlated with $rCMRO_2$ in the left sensorimotor cortex ($p < 0.05$) and mean cortical metabolic rate of oxygen ($mCMRO_2$, $p < 0.05$). Extensor plantar responses on the right ($p < 0.05$) and the left ($p < 0.05$) depended on the decrease in mCBF.

These data suggest that hypoperfusion and oxygen hypometabolism in the anterior cerebral hemispheres have an etiological relationship with the deterioration of intellect in patients with progressive dementia and ALS. The metabolic and perfusional changes in the cerebral cortex of ALS patients are likely to depend on upper motor neuron involvement, but they are not confined to the neurons of the corticospinal tract. Our study shows that PET is a powerful aid for us to distinguish MND-D from ALS without cognitive dysfunction. Future studies with PET or SPECT may discover a relationship between behavioral and psychiatric changes and their responsible brain regions.

In comparison with reports of brain imaging studies in the North American and European

populations,[22] our series seem to have no essential differences. According to a PET study[23] using FDG in the Korean population (relatively close to us geographically), all the MND-D patients showed glucose hypometabolism only in the frontal area, whereas most patients with FTD without ALS had hypometabolism in the frontal and temporal areas. MND-D also showed a more symmetric pattern of glucose hypometabolism than FTD without ALS. These findings are somewhat inconsistent with the report from Europe[22] showing hypometabolism in the bilateral frontal lobe, anterior temporal lobe, and putamen in MND-D patients. Compared with FTD without ALS, MND-D showed more hypometabolism in the bilateral temporal lobes. However, the discrepancy may be related to differences in sample characteristics in these studies and does not seem fundamental.

CONCLUSIONS

This clinical overview of FTD in the Japanese ALS population indicates that most clinical features are shared with those in the North American and European ALS populations.[24] Therefore, there are few rational reasons to consider that FTD in the Japanese ALS population is a distinctive entity. It is also very interesting that the Japanese population is ethnically homogeneous whereas the North Americans and Europeans appear multiethnic.

Recent pathological studies also demonstrate absorbing findings. Through the characteristic feature of ubiquitin-positive intraneuronal inclusions in the brain, FTD, MND-D and ALS[25] could be reassembled into an inclusive entity. Almost all typical MND-D, a considerable portion of FTD, and nearly 20% of ALS cases show that type of inclusion. There are several studies reporting that a considerable proportion of FTD patients show motor neuron signs or electrophysiological abnormalities indicating motor neuron involvement. Conversely, ALS patients often show cognitive dysfunction on appropriate neuropsychiatric examinations.[12] These clinical and pathological findings appear to indicate the presence of a common pathoetiological background.

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8

Primary lateral sclerosis: cognitive, language, and cerebral hemodynamic findings

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INTRODUCTION

This chapter focuses on the cognitive characteristics, language processes, and associated cerebral hemodynamic findings of patients with primary lateral sclerosis (PLS). PLS is a rare adult-onset motor neuron disease (MND) that was first recognized by Charcot in 1865[1] and further described by Erb in 1875.[2] The primary clinical symptom is progressive spinobulbar spasticity with a gradual and slow course.[3] There is an absence of family history and sex distribution is equal. Other common clinical symptoms, related to corticospinal dysfunction, include spasticity of all limbs, spastic bulbar symptoms (e.g. dysarthria, dysphagia), pseudobulbar affect, hyperreflexia, and bilateral Babinski signs. In contrast to amyotrophic lateral sclerosis (ALS), PLS has been defined traditionally as affecting only the upper motor neurons.[3] Lower motor neuron signs, including fasciculations and muscular wasting, are characteristically absent (or much less marked than in ALS). The classic symptoms of PLS are related to loss of precentral pyramidal neurons, secondary pyramidal tract degeneration, and relative preservation of anterior horn motor neurons.[4] Current diagnostic criteria (Pringle criteria)[3] require symptom duration of at least 3 years. Compared with ALS, PLS is typically a more benign process with a markedly longer disease duration (median of 19 years).[3]

Whether PLS is a distinct nosological entity or a variant of ALS is a long-debated controversy.[5] Although PLS has been differentiated as a disease separate from ALS,[3,6] its characterization as a distinct entity also has been challenged.[4,5,7,8] For example, Le Forestier et al.[4] presented both clinical and electrophysiological evidence indicating that although lower motor symptoms are less prominent in PLS compared with ALS, they are nonetheless quite common. In their sample of 20 patients with PLS, they found that the majority had symptoms of cramps (16 of 20 patients), fasciculations (18 of 20) and/or atrophy (12 of 20). Furthermore, denervation occurred in 14 of 20 patients. Another cogent argument against the distinctness of PLS from ALS is that many patients with PLS eventually progress to develop lower motor neuron symptoms similar to ALS.[5]

Based on these findings, several researchers propose that PLS should not be viewed as a discrete nosological entity but rather as a rare, predominantly upper motor neuron variant at one end of the spectrum of MND, with progressive muscular atrophy at the other end.[4,8] However, notwithstanding the overlap between the two diseases, a continuing distinction between PLS and ALS may be important due to the markedly different prognoses involved.[9]

Cognition in PLS

In contrast to ALS, in which cognitive impairment is now recognized as a common disease association, the evidence for cognitive impairment in PLS is much less established, due largely to the paucity of research in this area. Pringle and colleagues[3] asserted that cognitive functioning is not affected in PLS, noting that all eight of their patients had 'preserved intellect'. However, their conclusions were not based on cognitive testing. Thus although their patients did not demonstrate a florid dementia, more subtle cognitive impairment could have been present. In particular, deficits of a frontal nature could have been missed without formal and detailed testing. Other reports of normal cognitive functioning in patients with PLS also have been published.[10–13] However, these studies either lack neuropsychological testing or do not include adequate descriptions of the testing.

In contrast, several investigators reported cognitive impairment or dementia in case studies of patients with PLS.[8,14–16] However, to date, there have been few systematic examinations (i.e. group comparisons, longitudinal designs, etc.) of the neuropsychological features of the disease. The first methodical study was completed by Caselli and colleagues in 1995.[17] Due to the retrospective design of their study, not all patients (n = 9) were administered all tests. Results indicated mild cognitive deficits in the areas of executive functioning, psychomotor speed, and memory, consistent with subtle frontal deficits. The most sensitive test in their battery was the Controlled Oral Word Fluency test, a test of verbal fluency. Patients performed normally on tests of orientation, mental status, intellectual functioning, spatial skill, and language. None of the patients was judged to have dementia and the mild cognitive deficits generally were not of concern for the patients or families.

More recently, in an extensive longitudinal study of 20 patients with PLS, Le Forestier and colleagues examined clinical, electrophysiological, and pathological parameters.[4] Although only discussed briefly, neuropsychological results indicated that 16 of 20 patients exhibited moderate deficits in frontal and/or premotor functions compared with age- and education-matched controls. However, none of their patients demonstrated a global dementia and no correlation existed between the neuropsychological deficits and other clinical or pathological parameters.

Language in PLS

There are no published studies that describe specifically the language and communication of individuals with PLS. There is, however, emerging literature describing the language of individuals with ALS which, as noted earlier, is thought to be linked neurobiologically with PLS. There are two profiles of spoken output observed in ALS. The first includes aspontaneous language and economy of utterances (i.e. lack of initiation of conversation or reduced output characterized by short phrases or stereotyped utterances).[18,19] The second profile includes press of language (i.e. increased amount of spoken output) where individuals interrupt or monopolize conversations.[18] Other general spoken language characteristics in ALS include echolalia, mutism, perseveration,[18] stereotypic use of words, phrases or themes[20] and stereotypical word repetitions, with persistent repetitive errors.[19]

There is a consistent impairment in naming verbs versus naming nouns in individuals with ALS.[21–23] Verb deficits are linked to frontal lobe dysfunction, whereas noun deficits are linked to temporal pathology.[21] Further evidence of frontal lobe involvement in the language of individuals with ALS is based on their poor performances on verbal fluency tasks.[24–27] Difficulties naming nonliving items (e.g. tools) by individuals with ALS suggest frontotemporal pathology, based on findings from individuals with Alzheimer's disease (AD) where patients with AD experience

more difficulty naming living items.[28] Individuals with ALS also show problems with confrontation naming (i.e. word retrieval deficits).[26,29–32] Abrahams and colleagues[24] found that individuals with ALS but without dementia named significantly fewer objects than controls.

Additional specific language deficits in ALS include problems with auditory comprehension, spelling[29] and single-word vocabulary comprehension.[32] Individuals with ALS typically produce verbal paraphasias (e.g. 'table' for 'car') and semantic paraphasias (e.g. 'plate' for 'cup').[32] In addition, discourse analysis reveals that ALS patients correct themselves significantly less often than individuals without ALS.[32]

A PROSPECTIVE STUDY OF COGNITION, LANGUAGE AND CEREBRAL BLOOD FLOW IN PLS

In order to characterize cognitive and language functioning in PLS, we undertook a prospective study of a relatively large sample of patients with PLS (n = 18), meeting the Pringle criteria.[3] We examined a wide range of cognitive skills, with emphasis on executive processes. In addition, we assessed emotional and behavioral symptoms as this is a key area affected in frontotemporal dysfunction. A detailed language analysis also was performed. All patients underwent cerebral blood flow studies to examine the association between cognitive impairment and hemodynamic parameters. The mean age of participants was 58.4 (range 44–72 years, SD = 8.1); the mean educational level was 12.8 (range 8–18 years, SD = 3.0); and the mean disease duration was 9.4 years (SD = 7.0), ranging from 3 to 26 years. There were nine men and nine women.

Neuropsychological functioning in PLS

A neuropsychological test battery designed to minimize the need for speech production and upper limb motor skills was administered to all participants. The measures were categorized into five general domains of functioning with a particular emphasis on frontal-executive skills (Table 8.1).[33–44] Nine neuropsychological tests

Table 8.1 Neuropsychological tests and variables

Domain	*Test*	*Variables*
Executive skills	WCST	Perseverative responses Total errors
	COWAT	Number of words
	TWWF	Number of words
	DAT	Number of errors
Attention/concentration	CTT	Mean score of three trials
Visual-perception/ visual-construction	MFVPT-R	Number correct
	Block Design (WAIS-III)	Age-scaled score
Memory	RAVLT	Total words trials 1–5 Delay recall number of words Delayed recognition
	WRMT	Number of words correct Number of faces correct
Emotional/behavioral functioning	GDS	Total score
	NPI	Total score
	FBI	Total score

WCST, Wisconsin Card Sorting Test (one deck version);[33] COWAT, Controlled Oral Word Association Test;[34] TWWF, Thurstone Written Word Fluency;[35] DAT, Delayed Alternation Test;[36] CTT, Consonant Trigrams Test;[37] MFVPT-R, Motor-Free Visual Perception Test – Revised;[38] WAIS-III, Wechsler Adult Intelligence Scale – III;[39] RAVLT, Rey Auditory Verbal Learning Test;[40] WRMT, Warrington Recognition Memory Test;[41] GDS, Geriatric Depression Scale;[42] NPI, Neuropsychiatric Inventory;[43] FBI, Frontal Behavioral Inventory.[44]

were administered with a total of 13 variables analyzed. Three self-report questionnaires, involving three additional variables, also were used to assess emotional/behavioral factors. The Geriatric Depression Scale[42] was administered directly to patients. The Neuropsychiatric Inventory[43] and Frontal Behavioral Inventory[44] were administered to the participants' caregivers.

All scores were converted into T-scores (mean of 50, SD of 10) based on normative samples stratified for age and when available for education. A T-score < 40 (i.e. > 1 SD below the mean) on a specific measure was considered abnormal. A participant's overall performance on the test battery was defined as cognitively impaired if he/she demonstrated two or more abnormal scores on at least two different cognitive tests.

As a group, the PLS participants scored broadly within normal limits (mean T-scores > 40) on all cognitive measures. However, when the data were examined on a case by case basis, there was a considerable amount of heterogeneity. Specifically, four patients performed within normal limits on all measures, three patients performed in the abnormal range on one measure, seven patients performed in the abnormal range on two to four measures, and four patients scored in the abnormal range on five or more measures. In total, 11 of 18, or 61% of participants had cognitive impairment as defined in this study. When more stringent criteria for impairment were applied, i.e. two or more abnormal scores > 1.5 SD below the mean, 7 of 18, or 39% of participants had cognitive impairment. Finally, with the most stringent criteria of two or more abnormal scores > 2 SD below the mean, 4 of 18 patients, or 22% had cognitive impairment. It should be noted that these numbers may underestimate the level of impairment, since several participants did not complete all tests due to various factors (e.g. fatigue, inability to perform task, etc.).

Areas of cognition affected

The following tests identified impairment in patients (in order of most to least sensitive): Controlled Oral Word Association Test (50% impairment rate as defined by study criteria); Delayed Alternation Test (40% impaired); Rey Auditory Verbal Learning Test – total words learned (33% impaired); Consonant Trigrams Test (29% impaired); Warrington Recognition Memory Test – Faces (24% impaired); Wisconsin Card Sorting Test – both perseverative and total errors (22% impaired); Rey Auditory Verbal Learning Test – recognition (22% impaired); Thurstone Written Word Fluency (18% impaired); and Rey Auditory Verbal Learning Test – delayed recall (11% impaired). No patients were impaired on the following measures: Warrington Recognition Memory Test – Words; Motor-free Visual Perception Test – Revised; and Block Design.

Relationship between disease parameters and cognitive functioning

No relationship was observed between disease duration and cognitive functioning ($r = 0.077$, $p > 0.05$). With respect to current site of disease, there were 6 patients with limb-only symptoms and 12 patients with both limb and bulbar symptoms. In the limb-only group, three of six patients (50%) were cognitively impaired. In the limb and bulbar group, 8 of 12 patients (67%) were cognitively impaired. However, a t test between these groups revealed no significant difference ($p > 0.05$) in test performance. The data also were analyzed with respect to site of onset. There were 15 cases with onset of limb symptoms, and only 3 cases with onset of bulbar symptoms. In the limb-onset group, 9 of 15 patients (60%) were impaired, while in the bulbar-onset group, 2 of 3 patients (67%) were impaired. A t test between the groups did not reveal significant differences in test performance.

To rule out the effects of respiratory insufficiency on cognitive performances, respiratory variables were examined. The median forced vital capacity score of our participants was 91% and CO_2 values were all within the normal range.

Finally, cognitive performance was correlated with scores on the ALS Functional Rating Scale – Revised. The relationship was not significant ($p > 0.05$).

Results of emotional/behavioral measures

The mean Geriatric Depression Scale score was 8.3, considered within normal limits. Performance was within normal limits for 14 of 17 participants (82%) while only 3 participants fell in the depressed range. On the Neuropsychiatric Inventory, relatives of 8 of 14 participants (57%) identified symptoms considered outside the normal range. The following behavioral categories were endorsed (in order of frequency): depression/dysphoria (57%), nighttime behavior (36%), agitation (29%), appetite/eating changes (21%), irritability/lability (14%), apathy/indifference (14%), and aberrant motor behavior (7%). Finally, analysis of the Frontal Behavioral Inventory (FBI) responses indicated that no participants scored in the range of frontotemporal dementia (FTD). The most common symptoms endorsed by relatives ($n = 14$) were as follows: verbal apraxia (71%), irritability (57%), apathy (43%), logopenia (43%), alien hand (43%), inflexibility (36%), indifference/emotional flatness (29%), restlessness (29%), aggression (29%), hypersexuality (21%), and incontinence (21%). There were no significant correlations between the emotional/behavioral measures and overall cognitive functioning. However, of the four most severely cognitively impaired participants, two had the highest FBI scores.

Language functioning in PLS

Seventeen of the 18 participants with PLS underwent a detailed battery of language tests. One PLS participant was excluded from the analyses because she failed to meet inclusion criteria of English as her primary native language. The nine men and eight women PLS participants ranged in age from 44 to 73 years ($M = 58.2 \pm 8.2$), and their education ranged from 8 to 18 years ($M = 12.8 \pm 2.9$). All except two were right-handed. Eleven control participants (three men and eight women) also were recruited. There were no significant differences between the groups in age and education.

The modified, 30-item[45] Boston Naming Test (BNT)[46] and the 55-item Action Naming Test (ANT)[47] were administered to examine noun versus verb spoken naming. Raw scores from the BNT and the ANT were converted to z-scores to facilitate between and within group comparisons. A verbal fluency task was administered that included living (i.e. animals, birds, water creatures, dogs) and nonliving categories (i.e. household items, transportation, musical instruments, tools).[48,49] Participants were asked to generate as many exemplars as they could in 1 minute for each of the eight categories.

Overall, results indicated subtle differences between control and PLS participants. Independent t tests on verbal fluency per category (i.e. living and nonliving) demonstrated that PLS participants produced significantly fewer items than controls (t (27) = –2.77, $p = 0.01$). PLS participants produced a mean of 14.97 for each category whereas controls produced a mean of 17.38 per category. There were no significant differences between PLS participants ($M = 14.75$) and controls ($M = 16.55$) for items in the living category (t (27) = –1.32, $p = 0.27$). However, PLS participants ($M = 15.20$) produced significantly fewer nonliving items than controls ($M = 18.20$, t (27) = –2.75, $p = 0.01$). Pairwise comparisons revealed no significant differences within the PLS or control groups for living versus nonliving categories. A second set of independent t tests and pairwise t tests compared noun and verb confrontation naming in the PLS and control groups. Independent t tests revealed no significant differences between PLS participants versus controls for naming nouns (t (27) = 0.74, $p = 0.47$) and naming verbs (t (27) = 5.15, $p = 0.61$). Pairwise t tests showed that PLS participants (t (17) = –0.12, $p = 0.91$) and control participants (t (10) = 0.15, $p = 0.88$) did not have significant problems naming pictured nouns versus pictured verbs.

The relationship between cognitive functioning and cerebral hemodynamic findings in PLS

Previous imaging studies using magnetic resonance imaging (MRI) and computed tomography (CT) in MND focused on morphological changes that occur with disease progression.[3,9,50] However, recently it has been suggested that cognitive impairment in MND may be reflected by cerebral hemodynamic changes.[32] Positron

emission tomography (PET)[51,52] and single photon emission computed tomography (SPECT)[53] are functional neuroimaging techniques shown to be sensitive markers of cognitive impairment or frontotemporal dysfunction in ALS.

In our analysis, CT perfusion imaging (CT perfusion head scan using a four-slice CT scanner; GE LightSpeed Plus; GE Medical Systems, Milwaukee, WI, USA) was used to measure concomitant changes in cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) (Fig. 8.1). Imaging was conducted with the 18 PLS participants described previously and 7 non-PLS control participants (4 men and 3 women) whose ages ranged from 34 to 63 years (mean = 52.9 ± 9.2 years). PLS participants were stratified into three groups based on the number of abnormal neuropsychological test scores (defined as a performance > 1 SD below the mean). The number of abnormal test scores ranged from 0 to 6. Those participants who were unimpaired on all test scores (with 0 abnormal scores) were considered to be cognitively 'Normal'. PLS participants with one to three abnormal test scores were considered to have 'Mild' cognitive impairment. Finally, PLS participants with four to six abnormal test scores were considered to have 'Moderate' cognitive impairment. Hemodynamic parameters (CBV, CBF, and MTT) were compared within and between groups and correlation analyses were performed with the number of abnormal test scores.

We observed significant differences between groups for CBF and MTT. CBV was not significantly different between groups (Table 8.2). An ANOVA revealed no significant differences between the cognitively 'Normal' PLS participants, 'Mild' PLS participants, and controls for any measured parameter in any region in the gray matter ($p > 0.05$). MTT was significantly increased in the 'Moderate' group in all regions when compared with the control participants and 'Normal' PLS group ($p < 0.05$), with the exception of the temporal and occipital lobes in the 'Normal' group. CBF was significantly decreased in the 'Moderate' group in the occipital region when compared with controls and in the occipital and temporal regions when compared with the 'Normal' group ($p < 0.05$). CBF also was negatively correlated with abnormal cognitive scores in all regions of the brain, ranging from $-0.43 \leq r \leq -0.68$ ($p < 0.05$). MTT was positively correlated ($0.49 \leq r \leq 0.65$) with abnormal scores across all regions ($p < 0.05$). CBV was not significantly correlated with cognitive functioning (Table 8.3).

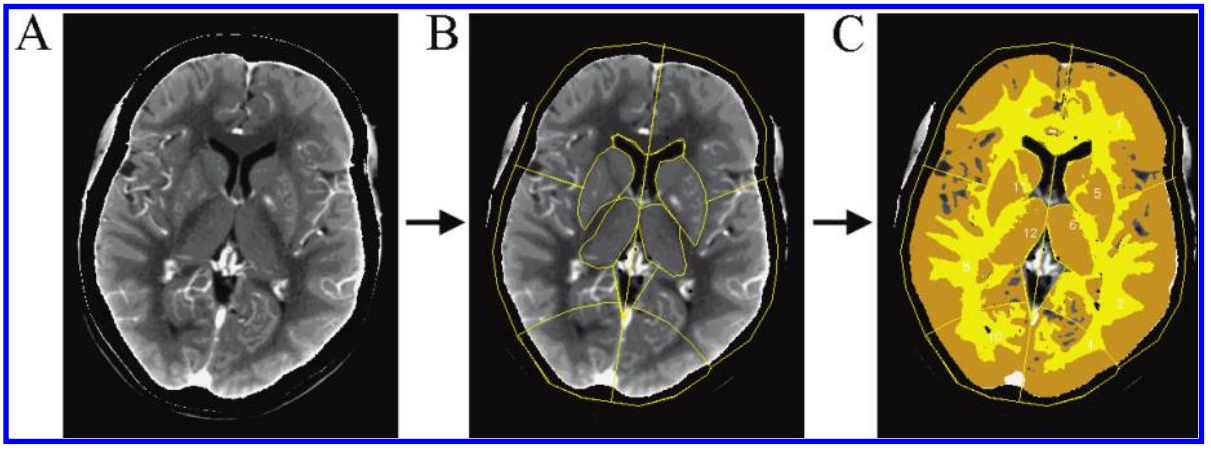

Fig. 8.1 Reconstructed CT images (A) were segmented into functional regions based on anatomical landmarks and sectional anatomy to produce the constituent lobes of the brain and deep gray matter structures (B). Further processing was done to segment the gray and white matter (C) based on the CT number for each pixel in the image. The templates produced in (C) were then superimposed onto all other hemodynamic maps to obtain CBF, CBV, and MTT values for the given regions.

Table 8.2 Comparison of gray matter cerebral hemodynamics between groups

		Control		*Intact*		*Mild*		*Moderate*			*Post hoc Tukey p-value*	
Parameter	*Region*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*ANOVA p-value*	*Control vs moderate*	*Intact vs moderate*
CBF	Frontal	38.7	3.46	40.9	3.04	39.2	5.08	34.7	2.13	NS	–	–
	Temporal	39.5	4.32	43.2	3.50	39.7	3.98	35.4	3.08	0.032	NS	0.021
	Parietal	44.2	4.82	44.9	2.14	40.5	4.15	38.0	6.09	NS	–	–
	Occipital	39.6	4.24	41.3	4.45	36.6	3.38	32.0	4.37	0.005	0.013	0.009
	Basal ganglia	40.5	5.94	44.7	2.12	39.1	2.34	37.2	4.55	NS	–	–
	Thalamus	37.6	6.04	40.0	4.89	37.1	4.45	31.7	5.24	NS	–	–
CBV	Frontal	1.52	0.17	1.60	0.05	1.76	0.25	1.72	0.09	NS	–	–
	Temporal	1.79	0.20	1.79	0.11	1.86	0.27	1.86	0.11	NS	–	–
	Parietal	1.82	0.31	1.69	0.07	1.87	0.34	1.98	0.12	NS	–	–
	Occipital	1.83	0.24	1.96	0.21	1.97	0.28	2.02	0.15	NS	–	–
	Basal ganglia	1.48	0.18	1.63	0.06	1.68	0.21	1.72	0.14	NS	–	–
	Thalamus	1.56	0.21	1.63	0.03	1.81	0.26	1.82	0.17	NS	–	–
MTT	Frontal	2.37	0.29	2.36	0.22	2.71	0.34	2.99	0.29	0.004	0.006	0.019
	Temporal	2.48	0.41	2.50	0.31	2.83	0.40	3.18	0.36	0.015	0.017	NS
	Parietal	2.47	0.34	2.27	0.19	2.77	0.39	3.18	0.37	0.003	0.011	0.004
	Occipital	2.82	0.60	2.88	0.49	3.25	0.53	3.83	0.47	0.014	0.013	NS
	Basal ganglia	2.22	0.28	2.19	0.17	2.58	0.30	2.79	0.28	0.004	0.010	0.020
	Thalamus	2.50	0.45	2.47	0.31	2.96	0.47	3.52	0.59	0.006	0.008	0.017

An ANOVA revealed significant differences ($p < 0.05$) between groups for CBF (cerebral blood flow) and MTT (mean transit time). No significance (NS) was determined for CBV (cerebral blood volume) between groups. Further *post hoc* Tukey analysis described where the differences between these groups originated with respect to region.

Table 8.3 Correlation of abnormal neuropsychological test scores with cerebral hemodynamics results

Brain region	*CBF*	*MTT*
Frontal	–0.54*	0.53*
Temporal	–0.51*	0.49*
Parietal	–0.44*	0.65**
Occipital	–0.68**	0.58**
Basal ganglia	–0.56*	0.54*
Thalamus	–0.53*	0.64**

Significant correlations for CBF (cerebral blood flow) and MTT (mean transit time) with the number of abnormal test scores (0–6) by brain region denoted by * $p < 0.05$ and ** $p < 0.01$. CBV (cerebral blood volume) did not correlate significantly with the number of abnormal test scores.

DISCUSSION

The neuropsychological data indicate heterogeneity among our participants with PLS. While some individuals showed impairment in numerous cognitive processes, other participants did not exhibit any cognitive impairment based on our research criteria. Similarly, heterogeneity was present with respect to behavioral and emotional symptoms, although a majority of PLS participants were characterized by their caregivers as having a high (i.e. abnormal) number of symptoms. For the majority of PLS participants, however, cognitive, behavioral and language symptoms were generally subtle and did not meet the criteria for FTD. Perhaps only 2 of our 18 patients could be classified as meeting the Neary criteria for FTD.[18]

Although not all our participants with PLS demonstrated deficits in cognitive functioning, cognitive impairment appears to be a common symptom of the disease, as it is with sporadic ALS. Using our relatively lenient definition of impairment, the majority of participants (61%) were classified as having at least mild cognitive impairment. Deficits were most prominent in the areas of executive functioning, working memory, and learning efficiency. Interestingly, the most sensitive measure in this study was oral word fluency, a measure that is reported repeatedly to be impaired in patients with ALS. This finding also is consistent with other published reports showing that verbal fluency is the most sensitive measure in detecting cognitive impairment in PLS.[17] Oral word fluency was followed by delayed alternation as the second most sensitive test to detect impairment in our study. The delayed alternation task is reported to measure prefrontal functioning, within both the orbitofrontal and dorsolateral regions.[54] Other executive measures that also were sensitive in detecting impairment were the Consonant Trigrams Test, a measure of working memory; the Wisconsin Card Sorting Test; and Thurstone written word fluency.

With respect to the language analyses, the fact that PLS participants produced significantly fewer exemplars for nonliving items than did controls on a measure of verbal fluency parallels, in part, findings for individuals with ALS. Rakowicz and Hodges[49] identified subgroups among 18 participants with ALS who exhibited impaired language function characterized mainly by word-finding difficulties and a decrease in verbal fluency. Impaired verbal fluency has been documented in a number of studies of participants with ALS, FTD and AD.[24–27,49] Documenting that individuals with PLS have more difficulty with nonliving items is of particular relevance given that individuals with AD experience greater difficulty on measures of verbal fluency for living items.[28] Differences in verbal fluency for nonliving versus living categories could provide further important diagnostic and neurolinguistic information on the nature of semantic memory differences among PLS, ALS, FTD, and AD groups.

Confrontation naming of nouns and verbs was relatively intact in the PLS participants. These findings are inconsistent, in part, with the findings of Bak and Hodges[21] who found that individuals with ALS are more impaired in naming verbs than naming nouns. Interestingly, other studies showed that selected groups of individuals with FTD, a condition observed in ALS, are more likely to experience difficulty naming verbs than naming nouns.[23] These findings suggest that there are differences in linguistic abilities between participants with PLS versus those with ALS. Alternatively, perhaps the differences between naming nouns and naming verbs are too subtle to be detected by the BNT and ANT. Future studies on noun versus verb confrontation naming should consider other measures such as verb naming from the *Psycholinguistic Assessments of Language Processing in Aphasia (PALPA)*[55] or the *Test of Adolescent/Adult Word Finding (TAWF)*.[56]

The primary finding from our cerebral hemodynamic study was that increased cognitive dysfunction was correlated significantly with decreased brain perfusion as measured by significant increases in MTT and decreases in CBF. One hypothesis to account for these results is that cognitive decline in PLS may be associated with activation of the cerebrovascular reserve, manifested as trends of increasing CBV and decreasing CBF.[57,58] MTT is equal to CBV divided by CBF, thus, an increase in CBV and decrease in CBF results in an amplification of the change in MTT. The most cognitively impaired patient group in this study had significant global increases in MTT when compared with cognitively normal controls. The trend of decreasing global CBF is consistent with the current literature describing global decreases in CBF in cognitively impaired ALS patients when compared with controls and ALS patients without cognitive impairment.[59] These data suggest that PLS patients are subject to hemodynamic compromise associated with cognitive decline, not unlike that seen in ALS.

In summary, our study and those of previous authors suggest that cognitive dysfunction may in fact be a relatively common feature of PLS. The spectrum of deficits observed in PLS is consistent with that observed in ALS, although

the magnitude of deficit may be lower. The clinical implications of these deficits remain to be fully explored. With respect to the issue of whether ALS and PLS are the same or separate entities, the observations that cognitive, language, and blood flow characteristics are similar between the two diseases suggests a continuum of disease. We would further suggest that cognitive dysfunction in both PLS and ALS reflects a dysexecutive syndrome resulting from dysfunction of frontal lobe circuitry. More interdisciplinary research is needed to further elucidate the relationship between these two similar diseases. In particular, direct comparison between individuals with ALS and PLS on cognitive and language measures would further help to address these questions.

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9

The anatomic basis of symptoms in frontotemporal dementia

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INTRODUCTION

A behavioral syndrome and two language variants are typically described in frontotemporal dementia (FTD).[1,2] The syndromes are defined clinically by the presence of particular symptoms, which reflect the distribution of the underlying pathology involved. In FTD associated with ALS (FTD-ALS), several of these symptoms are quite prominent. An understanding of their anatomic basis is facilitated by an appreciation of the different patterns of regional atrophy in these syndromes, together with an awareness of the normal functioning of the brain regions they affect.

FRONTOTEMPORAL SYNDROMES

Behavioral variant FTD

The behavioral syndrome (known variously as FTD, bv-FTD or fv-FTD) comprises a symptom cluster including apathy, disinhibition, aberrant social behavior, a lack of empathy, alteration in eating behavior, and the development of motor and verbal stereotypies. This variant of FTD is typically associated with frontal lobe damage, and there is evidence to suggest that the right hemisphere (including the right temporal lobe) is particularly important.[3–5]

Routine structural imaging can be normal early in the course of the disease, but volumetric assessment, using both manual tracing methods and automated techniques, such as voxel-based morphology (VBM), has shown involvement of the orbitofrontal (or ventromedial), anterior cingulate and dorsolateral prefrontal cortex.[6–9] This local atrophy correlates with behavioral indices.[5,9] Functional imaging changes using positron emission tomography (PET) are generally more extensive than structural alterations, with ventromedial and dorsolateral prefrontal hypoperfusion.[10–13] Pathological studies suggest that orbitofrontal and medial frontal regions together with the hippocampus are involved first, with subsequent extension of the process to involve other anterior frontal regions, the temporal cortices and the basal ganglia.[14,15] Eventually marked atrophy is seen in all brain regions.

The orbitofrontal cortex (OFC) has a significant role in the representation of reward. The secondary taste association cortex, which receives inputs from diverse regions of cortex including visual, somatosensory and olfactory areas, is situated in its posterior aspect. Neurons in the OFC respond differentially to particular tastes, and are active in a way that signifies the reward value of food.[16,17] The ability of this

region to form cross modal associations allows rapid coupling of external stimuli with a primary reinforcer (reward). Although strong associations are easily formed, the system is dynamic, and representations reflect the current reward value of stimuli based, in part, on internal homeostatic demands. Satiety is one such homeostatic modifier, and may decrease the responsivity of these neuronal assemblies. Damage to the OFC may impair these normal taste–reward–satiety relationships, and emerge as overeating – one aspect of abnormal eating behavior in FTD.

Reward representations are by no means all related to taste, and it appears that a hierarchy of rewards is represented in the OFC. Moving rostrally, the level of abstraction increases and concepts such as the reward value of money are represented.[18] A medio-lateral gradient also seems to exist, with the medial OFC concerning itself with reward, and lateral aspects being associated with punishment.[19]

In patients with focal brain lesions of the OFC, the level of social disinhibition correlates with the size of lesions in the orbitofrontal region.[20] Anger recognised in the faces of others is usually a strong stimulus for reversing inappropriate behavior, and elicits activity in the lateral orbitofrontal cortex in functional imaging experiments.[21] Patients with FTD and orbitofrontal lesions are significantly impaired in their ability to change behavior when reward contingencies change,[22,23] which may explain their failure to respond to such normal social signals of disapproval. There is often a distinct dissociation in these individuals between an intact knowledge of social rules, and the ability to actually apply them in daily life.[24]

Environmental dependency is another manifestation of orbitofrontal dysfunction, and patients are often unable to resist touching or fiddling with objects that come into view.[25] More extreme examples of this include imitation and utilization behaviors where actions of the examiner are copied, or attempts are made to use objects despite it being inappropriate to do so[26] (such as putting on a second pair of spectacles over a first pair). Such marked dysfunction is seldom seen early in FTD, but when present, it is often associated with other frontal release signs such as grasp, pout or palmomental reflex, which in turn suggest involvement of motor and premotor regions.[27]

Apathy is a common feature in FTD syndromes, and recent imaging studies implicate atrophy or dysfunction of either the anterior cingulate or dorsolateral prefrontal cortex.[5,11] In lesion studies, profound apathy is seen in bilateral anterior cingulate and ventromedial cortical damage, and in its extreme form produces the syndrome of akinetic mutism. Atrophy of the anterior cingulate and left premotor regions has been linked to the presence of aberrant motor behavior in FTD.[5]

Reciprocal connections between the dorsolateral prefrontal cortex and the parietal cortex form part of a system subserving working memory and attention. Executive function, an ability encompassing skills such as being able to shift attention between stimuli, resist interference and inhibit responses, plan ahead, problem-solve and make inferences, is impaired by dysfunction in this region of cortex or its subcortical connections. Perseveration is a further consequence of damage to structures in this area of the brain.

Language syndromes

Language can be profoundly affected in frontotemporal dementia. Classically, two syndromes are recognized: a syndrome of impaired fluency and syntax known as progressive nonfluent aphasia (PNFA), and a fluent syndrome where semantic memory (knowledge of facts or memory for words, people and places) is degraded, which characteristically produces anomia, and word-finding difficulty. The language syndrome in FTD-ALS seems to be predominantly a nonfluent syndrome affecting word production and syntax, but semantic impairment is also seen.[28–30]

Progressive non-fluent aphasia (PNFA)

In PNFA, a progressive deterioration in the fluency of speech occurs. Grammatical and phonological errors, combined with impairments in multisyllabic word repetition are the clinical hallmarks of this syndrome, with the

burden of pathology appearing to lie in the inferior frontal and anterior insula regions.[31]

The word 'nonfluent' may refer to a number of speech changes in PNFA. Early on, almost all patients begin to manifest reduced conversation ability and speak in shorter sentences. Others have effortful, labored speech and frank phonological errors which is sometimes due to so-called speech apraxia, an impairment in the motor planning and sequencing of the movements necessary for correct articulation. It leads to stuttering over the initial consonants of a word, hesitation in mid-word, and a breakdown of normal speech rhythm and stress. Other patients have marked dysarthria with orobuccal apraxia, and may initially have much better written communication. Eventually these patients will become monosyllabic or even mute, although this state takes several years to evolve.

Structural imaging shows widening of the Sylvian fissure with atrophy of insula, inferior frontal and superior temporal lobes. Recent studies using voxel-based morphometry (VBM) in patients with PNFA, defined by having either apraxia of speech and/or deficits in processing complex syntax, show consistent atrophy of the left inferior frontal and insular cortex[31,32] with more extensive dorsolateral prefrontal and perisylvian hypoperfusion on FDG-PET.[31]

Semantic dementia (SD)

SD develops when the pathology targets the temporal lobes. There are distinct differences between predominantly left and right variants, but invariably both temporal lobes are involved. When left-sided pathology is dominant, semantic knowledge (knowledge of facts about people, places and things) is particularly disrupted. The clinical features are of a progressive anomia associated with difficulty reading and spelling irregular words. Another key impairment, mirroring anomia, is a deficit in single-word comprehension, whether spoken or written. As a disorder of concepts and categories, SD also affects knowledge of object use. Other cognitive abilities are intact (visuospatial, perceptual, non-verbal problem-solving), but behavioral features are common. Language-related features, namely word-finding difficulty and impaired comprehension, are significantly more common in left-predominant SD.

By contrast, right-predominant cases show a higher prevalence of person recognition problems, social inappropriateness and poor insight into their condition.[33] Major personality changes with a tendency towards rigidity, loss of empathy and occasionally bizarre delusions may also be a feature of right-sided cases,[34–36] and new religiosity and eccentricity of dress is also reported.[3] Although this variant, which has only one-third the prevalence of left-sided cases, seems to be more convincingly associated with behavioral disturbance than the left,[3,33,37,38] cases are seldom, if ever, purely unilateral. After an average of 3 years, the symptoms that were not present initially have generally emerged, whether they be behavioral or semantic.[38]

The behavioral and personality changes associated with bv-FTD are frequently seen in SD, at presentation as well as later in the illness, but the emphasis is different. Here, impaired social functioning results from a combination of emotional withdrawal, depression, disinhibition, irritability, and changes in eating behavior as the development of a sweet tooth. There is more likely to be a restriction of food preferences, or bizarre food choices, rather than the overeating seen typically in bv-FTD. This probably relates to the progressive deficit in semantic knowledge about food. Loss of physiological drives is common and includes poor appetite, weight loss and decreased libido. Lack of empathy is a feature that appears to be more common as a later feature in disease, although it may be seen at presentation if this is delayed. Mental inflexibility can be quite extreme and can provoke marked behavioral fluctuations in response to changes in the immediate environment. Many patients seem to have a particular interest in word games, puzzles and writing notes.

In contrast to the behavioral syndrome (bv-FTD), the MRI is virtually always abnormal in SD, with readily apparent asymmetric anterior temporal lobe atrophy clearly visible on coronal images.[33,39] Recent volumetric studies (using both automated voxel-based morphometry and manual volumetry of defined anatomical structures) have refined knowledge of the distribution of brain atrophy, and confirm the

profound involvement of the temporal pole, fusiform gyrus and inferolateral temporal cortex. In virtually all cases these changes are bilateral and in some cases the right is more severely affected.[7,40–42] The hippocampus is also involved despite earlier reports of hippocampal sparing,[42] and may actually be more marked on the left than in Alzheimer's disease patients.[40,41] In SD, there is both lateralized and anterior-posterior (rostral > caudal) asymmetry. The temporopolar cortex is cytoarchitectonically continuous with the perirhinal cortex, which occupies the banks of the collateral sulcus and medial aspect of the temporal lobe, and should be considered as part of the same cortical region in terms of connectivity. Thus it is the temporopolar-perirhinal cortex which is severely affected in SD,[43] and performance on tests of semantic memory and naming correlate with its residual volume.

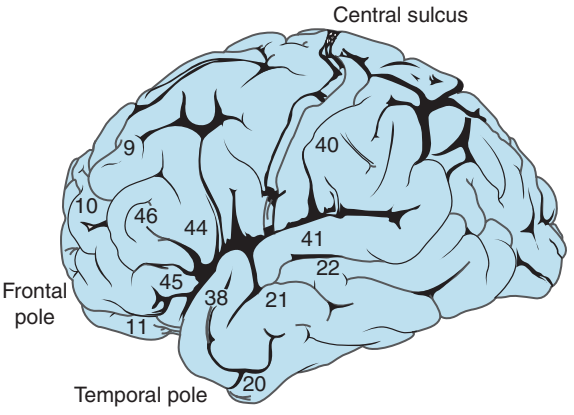

Fig. 9.1 Lateral aspect of cerebral cortex, labelled with Brodmann areas (BA): Broca's area (BA 44, 45), orbitofrontal cortex (BA 11), dorsolateral prefrontal cortex (BA 9, 46), anterior frontal regions (BA 9–11), temporopolar region (BA 38), inferior, middle, superior temporal areas (BA 20–22), supramarginal region (BA 40).

Regional dysfunction in frontotemporal syndromes

Imaging and pathological studies in FTD show damage not only to regions of the frontal and temporal cortices, as the name suggests, but also a number of other cortical and subcortical structures. The insula, amygdala, hippocampus and basal ganglia structures are also involved from relatively early in the disease process,[14,15] together with circuits that link these areas together.

Cortical and subcortical circuits (Figs 9.1 and 9.2)

There are extensive connections between different regions of the cortex that have similar levels of organization or differentiation. The simplest are the *limbic* areas which include the amygdala, hippocampus and primary olfactory (piriform) cortex. At a more complex level of differentiation, the *paralimbic* cortex includes the posterior orbitofrontal regions (BA 11–13), anterior cingulate (BA 23, 32), insula cortex (BA 14–16), the temporal pole (BA 38) and the parahippocampal cortices. More extensively laminated, i.e. differentiated, regions include the *heteromodal* association areas which receive neural inputs from the major sensory modalities, paralimbic regions and other heteromodal regions within the brain. The dorsolateral prefrontal (BA 45–47) and anterior frontal regions (BA 9–10, 11–12) are heteromodal.[44]

The cortex is also extensively linked to subcortical regions in the basal ganglia and thalamus. Five frontal-subcortical circuits have been described, all with a similar basic structure.[45–47] Prefrontal cortical regions project to the basal ganglia, then to the thalamus, and to complete the circuit project back to the frontal lobe region concerned. In the basal ganglia there are two further pathways; direct and indirect. In general, disruption of the direct pathway causes abnormal inhibition of thalamic output, whereas the indirect pathway disinhibits the response, and results in thalamic hyperactivity in turn influencing cortical function. The circuits operate in parallel, and there are connections between adjacent circuits, and both afferent and efferent projections with other cortical regions.[48] Three of these circuits have distinct relevance to FTD syndromes.

The *dorsolateral prefrontal circuit* projects from the anterior frontal lobe (BA 9,10) to the dorsolateral head of the caudate nucleus, and thence to the ventral anterior and mediodorsal thalamic

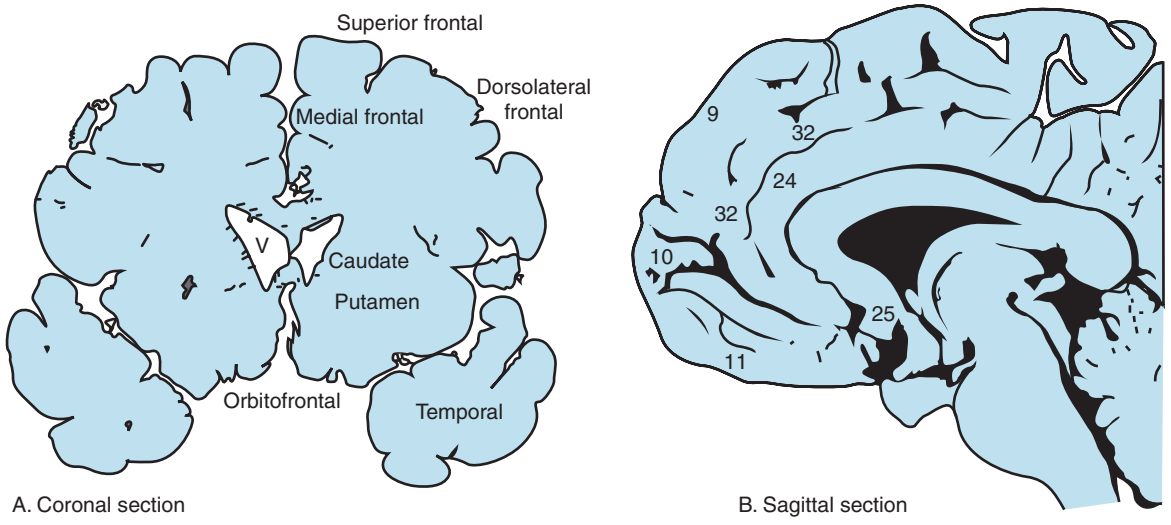

Fig. 9.2 Coronal section (A) showing subdivisions within prefrontal cortex and relationship to basal ganglia structures, and sagittal section (B) showing Brodmann Areas (BA) on medial surface of cortex. Superior frontal (BA 9), Frontopolar (BA 10), Orbitofrontal (BA 11), Anterior cingulate (BA 24, 32), Subgenual region (BA 25).

nuclei via the mediodorsal globus pallidus interna and substantia nigra. The dorsolateral region of the frontal lobe is involved in problem-solving, shifting attention, planning and organizational skills, which are the executive function skills referred to earlier.

The *orbitofrontal circuit* is involved in regulation of behavior. Lesions in the structures associated with this circuit (BA 10, 11, ventromedial caudate) may result in disinhibition, irritability, inability to adequately sense social cues, and deficits in recognizing and responding to emotions in others. Despite quite marked impairments in social conduct, if damage is limited to the orbitofrontal region, there may be few, if any, deficits on many formal tests of cognitive function.

The *anterior cingulate circuit* connects the anterior cingulate (BA 24, 25, 32) on the medial aspect of each frontal hemisphere to other parts of the limbic system. Apathy is often a prominent feature of damage to this region, most marked in the syndrome of abulia or akinetic mutism.

Separation of these circuits is maintained in a broad sense although there are connections that link circuits together. Focal lesions in corresponding regions of the basal ganglia or thalamus can produce similar syndromes to each of those just described. Note should also be made of the ascending projections from brainstem nuclei, which provide a further level of influence on prefrontal function and cortical-subcortical connections. Dopamine, serotonin, norepinephrine and acetylcholine networks all play a moderating role.[49]

Attempts to tightly localize particular cognitive or behavioral phenomena to specific brain regions are likely to come undone. Frontal and subcortical regions interact, and are part of distributed networks as discussed here. Focal damage to one part of the network may produce similar deficits to damage in another part, and distributed lesions may mimic more focal ones, particularly when taking into account levels of cortical redundancy.

FTD-ALS

Patients who present with cognitive symptoms in this syndrome typically have a combination of behavioral changes and aphasia,[50] which progress rapidly, followed by the emergence of bulbar features and limb amyotrophy, although the reverse sequence can be seen. A significant number of patients with MND show features of

dementia and/or aphasia if such features are systematically elicited.[51,52]

Patients with the MND-dementia/aphasia complex have disproportionate impairment of verb, compared to noun, knowledge, and have particularly marked pathological changes in the inferior frontal cortex (Brodmann areas 44 and 45, i.e. Broca's area).[30] This is supported by the results of a recent voxel-based morphometry study in which the middle and inferior frontal gyri were disproportionately atrophied in FTD-ALS compared with pure ALS or controls.[53] Furthermore, lesion studies and functional imaging experiments have shown dissociations in the representation of verbs and nouns in the cortex, with knowledge of verbs being particularly associated with inferior frontal regions.[54,55]

Our experience in Cambridge of 15 cases also suggests that psychotic phenomena are unusually prevalent in this subgroup,[30] in contrast to other forms of FTD.[56] However, they are fleeting in duration, and tend to predominate in the early stages when the behavioral syndrome is prominent. The explanation for this is unclear, but may be a consequence of rapid tissue destruction, and the sequence of functional disconnection between different cortical areas.[57] The remainder of the behavioral and cognitive features are indistinguishable from classical FTD, with disinhibition being particularly common.[58] From a practical perspective, this variant of FTD should be suspected in any cases with rapidly progressive disease or the emergence of bulbar symptoms.

CONCLUSION

Pathology in the frontotemporal syndromes is heterogeneous despite similar clinical presentations.[59] It is the distribution, rather than the nature of the underlying pathology, that produces individual symptom clusters. An understanding of regional cortical specialization and connections facilitates both pathological localization and improved clinical diagnosis.

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10

Neuroimaging in ALS and ALS with frontotemporal dementia

Erik P Pioro

INTRODUCTION

In the clinical evaluation of a patient with suspected amyotrophic lateral sclerosis (ALS), neuroimaging, mostly by magnetic resonance imaging (MRI), has been used to primarily identify treatable conditions mimicking ALS. Recently, however, there has been a growing interest in identifying anatomic changes, particularly intracranial, which are more specific for ALS and whose presence may assist in the diagnosis. In addition, the recognition in some patients of co-existing cognitive impairment or dementia arising from frontotemporal lobe degeneration, has raised the awareness of extramotor involvement in ALS and the increasing importance of imaging to detect such involvement.

This chapter will focus on how MR-based (and nuclear medicine-based) techniques have been useful in (1) revealing lesions of the motor pathway that support the diagnosis of ALS, (2) identifying cortical brain changes in motor and nonmotor regions of patients with ALS with or without coexisting frontotemporal dementia (FTD), and (3) revealing subcortical abnormalities along corticospinal tract (CST) and nonCST pathways in ALS patients by using nonconventional MRI techniques. Not only do these techniques have the potential to assist in the accurate and timely diagnosis of ALS with and without FTD, but they may provide insights into disease mechanisms and potential for therapeutic intervention.

CONVENTIONAL MAGNETIC RESONANCE SEQUENCES IN ALS

Hyperintensity of the corticospinal tract

The most characteristic neuroimaging finding in ALS is a hyperintense (increased) signal along the CST (or pyramidal tract) on T2-, proton density-, and fluid-attenuated inversion recovery (FLAIR)-weighted MRI. This abnormality, which is bilaterally symmetrical and more frequently detected in the cerebrum than in the spinal cord, probably represents wallerian degeneration of the CST, although only one study has examined this with post-mortem pathologic correlation.[1] Although CST hyperintensity can occur in any condition which results in upper motor neuron (UMN) injury, its symmetrical occurrence in the appropriate clinical setting is highly suggestive of UMN degeneration in ALS. However, an estimated 53–76% of normal individuals are found to have a small area of hyperintensity in the posterior

limb of the internal capsule on T2-weighted[2–5] and FLAIR-weighted[6] MRI sequences. This finding in normal brains, which probably results from the large-diameter myelinated axons of the CST,[1] appears faint, well circumscribed, limited to the internal capsule-cerebral peduncle regions, and is absent on proton density sequences MRI[3–5] (Fig. 10.1).

There have been numerous reports of subcortical white matter hyperintensities in the brains of patients with ALS, the first being almost 20 years ago by Goodin and colleagues.[2–4,6–13] Hyperintensity of the CST can be seen on T2- and proton density-weighted MRI along its intracranial extent from its origin beneath the cortical layer (centered on the primary motor cortex), through the corona radiata, centrum semiovale, posterior limb of the internal capsule and into the ventral brainstem (Fig. 10.2). Hyperintensity of the CST is most easily identified in the internal capsules and cerebral peduncles but is rarely seen in the lower brainstem.

Depending on the study, the reported frequency of such CST hyperintensity in patients with ALS ranges from 17% to 100%. Similar changes have been observed in other forms of motor neuron degeneration, including primary lateral sclerosis (PLS), familial ALS, and juvenile-onset ALS.[14] The wide range of occurrence may reflect a referral bias in the patient population studied or may represent technical limitation of detection. Alternatively, CST hyperintensity may occur in a specific subset of

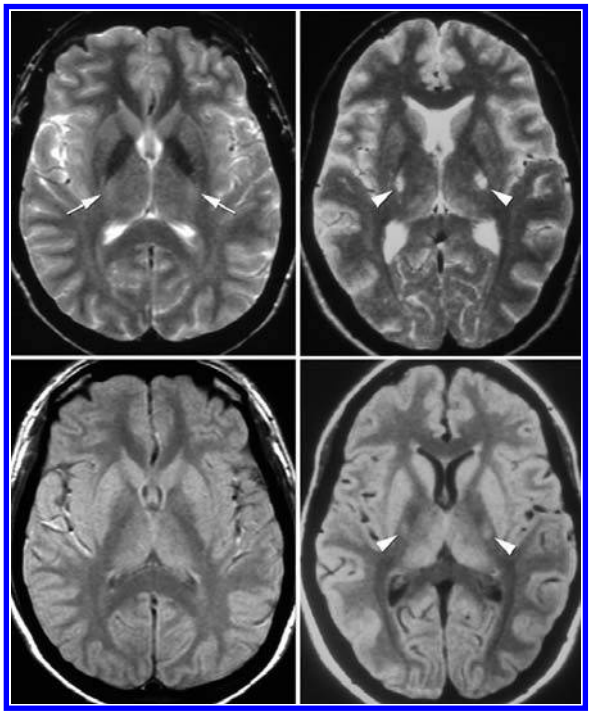

Fig. 10.1 A faint hyperintensity is occasionally detected on transverse T2- (arrows, top left) but not on proton density- (bottom left) weighted MRI in the posterior third of the posterior limb of the internal capsule (PLIC) in healthy individuals. This is in contrast to prominent hyperintensity seen in the PLIC (arrowheads) in a patient with ALS on T2-weighted (top right) and proton density-weighted (bottom right) sequences.

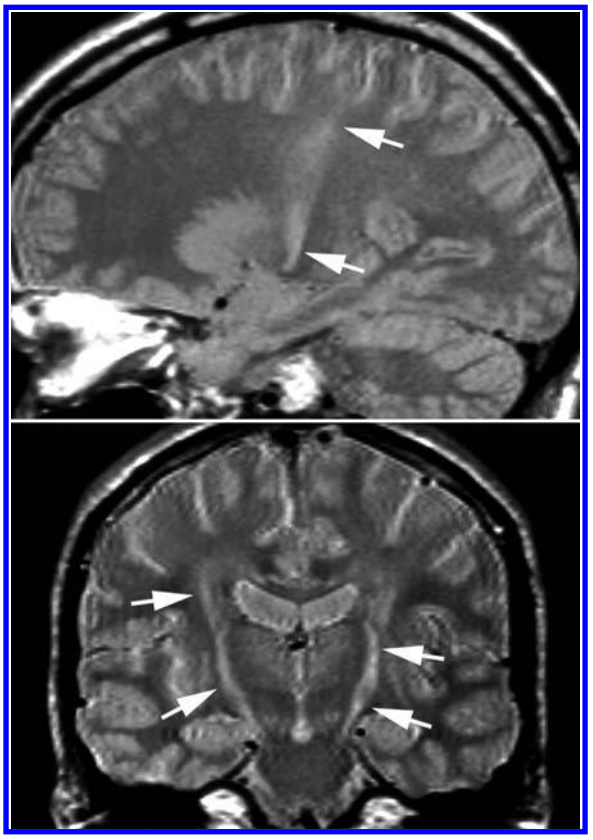

Fig. 10.2 Corticospinal tract hyperintensity in a 35-year-old man with upper motor neuron (UMN)-predominant ALS is noted on proton density-weighted sagittal (top) and coronal (bottom) MR brain images extending from the subcortical region to the internal capsule (arrows).

patients with ALS. Analysis of patient characteristics in previous reports revealed a higher number of younger patients who were usually female, with prominent UMN features (e.g. spasticity, hyperreflexia, Babinski reflex), and a more rapid initial decline, although not necessarily a shorter duration of disease (see Mitsumoto et al.[4] for references). However, no statistically significant differences were noted between the two groups for all of these features except age, *t* test assuming unequal variances. ALS patients with CST hyperintensities were significantly ($p < 0.001$) younger (50.7 ± 11.0 years, mean ± SD, $n = 42$) than those without such MRI abnormalities (59.0 ± 10.7 years, $n = 74$).[4] Although this may be due to ascertainment bias because younger patients with ALS tend to have brain MRI obtained more readily, it may represent a patient subgroup with earlier-onset disease. In a series of 110 consecutive patients with ALS who underwent MRI at the Cleveland Clinic, we found 17% ($n = 19$, 3 females, 16 males) to have only hyperintense signal along the CST, and an additional 10% ($n = 11$, 7 females, 4 males) with both this and hypointensity of the primary motor cortex, as discussed below. Of note, males outnumbered females 2:1 in our series of ALS patients with CST hyperintensity (either with or without cortical hypointensity).

Hyperintensity of the CST on T2-weighted MRI does not always correlate with prominent UMN signs, however, because patients with PLS, a motor neuron disease (MND) prominently affecting only UMNs, do not usually demonstrate this change. For example, one MRI study that compared 8 patients with PLS to 31 with ALS did not reveal CST hyperintensity, despite 7 patients with PLS showing marked spasticity and hyperreflexia.[15] The number of patients with no, mild or moderate hyperintensity (as defined by the authors) was essentially the same in both groups and marked CST hyperintensity was detected only in patients with ALS (10%). In another study of 10 patients with PLS, only 1 showed increased T2 signal in the posterior limb of the internal capsule extending into the corona radiata.[16]

FLAIR sequences have been reported to increase detection of brain lesions in a variety of neurologic diseases.[17,18] Because of technical limitations probably related to cerebrospinal fluid (CSF) pulsation, lesions in the brainstem are poorly visualized on FLAIR imaging.[18] A study of 31 patients with ALS and 33 healthy individuals compared the ability of FLAIR-, T2-, proton density-, and T1-weighted sequences to detect cortical and subcortical abnormalities.[19] Signal changes were graded visually by two blinded observers, based on surrounding brain tissue, as isointense, mild or distinct. FLAIR sequences appeared to be superior to T2- and proton density-weighted sequences at detecting hyperintensity in patients with ALS at the rostral extent of the CST, i.e. at precentral gyrus and centrum semiovale levels (Fig. 10.3). On the other hand, at caudal levels of the CST, beginning at the internal capsule, FLAIR sequences revealed nonspecific hyperintensity (mild or distinct) that was seen even in control individuals.[19] A quantitative analysis was also applied to the CST region to derive a 'contrast to noise ratio' (CNR) and this was found to be higher in FLAIR images than in all other sequences. The presence of hyperintensity on FLAIR did not correlate with the extent of UMN dysfunction, El Escorial classification, or duration of disease. When scans were separated by site of onset, however, patients with spinal-onset ALS had significant correlation of El Escorial criteria to hyperintensity in the

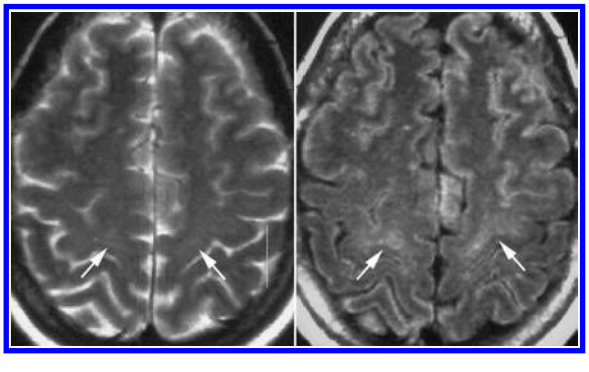

Fig. 10.3 Hyperintensity of the corticospinal tract at the level of the subcortical precentral gyrus in a 66-year-old patient with ALS appears faint on the T2-weighted MRI (arrows on left) but is more evident on the FLAIR sequence (arrows on right). Adapted from Hecht et al.[19] with permission from Elsevier.

sub-cortical precentral gyrus ($r = 0.461$, $p < 0.05$). Follow-up MRI in 17 of the original patients 15.7 ± 3.0 months after the initial evaluation showed no significant change in CST hyperintensity visually. However, there was a significant increase in quantitative FLAIR-CNR values of the subcortical precentral gyrus region between the first (4.57 ± 1.5) and second (6.03 ± 1.6) examinations ($p = 0.002$). This did not correlate with clinical parameters, although there was progression in the extent of UMN signs and El Escorial scoring.

Hypointensity of the neocortex

Normally on T2-weighted and FLAIR MRI, the neocortical gray matter is relatively hyperintense to the subjacent white matter. However, in some patients with ALS, it has a hypointense (diminished) signal. With T2-weighted sequences, 12–93% (median = 52%) of patients with ALS have been reported to have a bilateral ribbon-like hypointensity of the cortical margin in the precentral gyrus and occasionally in the postcentral gyrus.[4,6,8,10,13,19–22] The band-like hypointense signal in transversely oriented images near the vertex is rather obvious because of the hyperintense signal of CSF in adjacent sulci (Fig. 10.4). Unlike hyperintensity of the CST, hypointensity of the neocortex may be better visualized on T2-weighted images than in FLAIR images.[19,21] However, another study reported that the dark line in motor cortex in FLAIR- rather than T2-weighted images had high (74%) sensitivity but relatively low specificity (67%) in 18 patients with ALS compared with 18 age-matched normal controls.[23] No correlation was found between the appearance of the dark line and disease progression over 14 weeks in six patients with serial MRI.

Follow-up imaging of ALS patients demonstrated an increase in neocortical hypointensity on T2-weighted MRI from 12% to 35% ($p < 0.05$) after approximately 16 months.[21] Its cellular basis is uncertain but it reflects a shortening of the T2. One post-mortem study revealed iron-laden astrocytes and macrophages in the precentral cortex of such brains.[24] Because oxidative stress and nitrosyl groups also shorten T2,[25] this could also cause such signal change in ALS neocortex. The same report indicated that 4 of 15 ALS patients with ALS (27%) had combined cortical hypointensity and CST hyperintensity.[24] In our series of 110 consecutively imaged ALS patients, 10% ($n = 11$, 2 females, 9 males) had only hypointensity of the primary motor cortex. With the additional 10% that had both this and CST hyperintensity, as indicated above, just over two-thirds of the 20% of patients with this change were males.

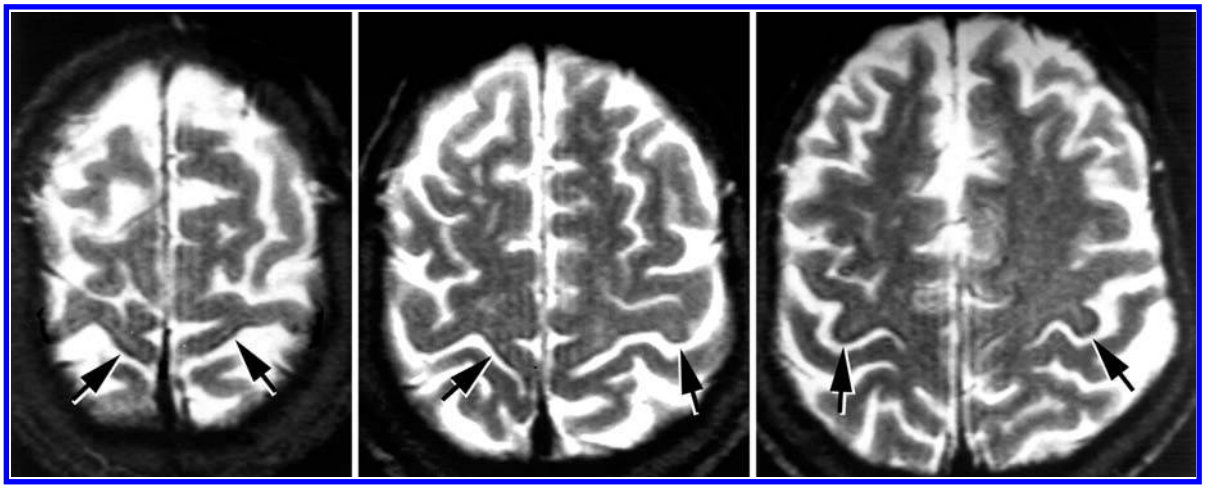

Fig. 10.4 Three transverse T2-weighted images near the vertex reveal a thin band-like hypointensity along the posterior margin of the precentral gyrus (primary motor cortex) in a 54-year-old man with ALS (arrows). Note that the subcortical white matter of this gyrus is faintly hyperintense relative to white matter in adjacent gyri.

However, this MRI abnormality can occur in patients with other neurodegenerative diseases, including Alzheimer's disease, multisystem atrophy, Parkinson's disease and progressive supranuclear palsy[26,27] and even in healthy individuals.[6,10,28,29] Although this may limit its specificity, a diminished signal in the primary motor cortex on T2-weighted and FLAIR MR images of patients presenting with features of ALS is supportive of the diagnosis, especially when occurring with CST hyperintensity.

Brain atrophy in ALS patients with or without dementia

Brain atrophy revealed by neuroimaging has not been generally thought to be a component of ALS or MND unless accompanied by dementia. However, few imaging studies in the past had carefully compared the frequency of brain atrophy in patients with ALS and age-matched controls. Most, but not all, reported some degree of atrophy,[4,30–36] which is consistent with post-mortem analyses showing variable amounts of atrophy.[37] Discrepancies in findings between these studies may relate, in part, to the analytic methodologies used, whether the atrophy involved motor or extramotor regions, and the presence or absence of overt dementia. In addition, earlier imaging studies usually did not include careful neuropsychological evaluations of patients who were not clinically demented but may have had milder degrees of cognitive impairment. Such patients may also have cortical or subcortical atrophy of extramotor regions. Patients with ALS and prominent FTDs, however, will usually have obvious cortical or subcortical atrophy. For example, a 62-year-old man with a 10-year history of progressive FTD underwent MRI when he began having worsening muscle weakness and wasting and a diagnosis of MND was entertained. Profound cortical and subcortical atrophy of frontal and temporal lobes was visualized (Fig. 10.5) and proven post mortem about 6 months later to be due to ubiquitin-positive, tau- and synuclein-negative MND-inclusion dementia.[38]

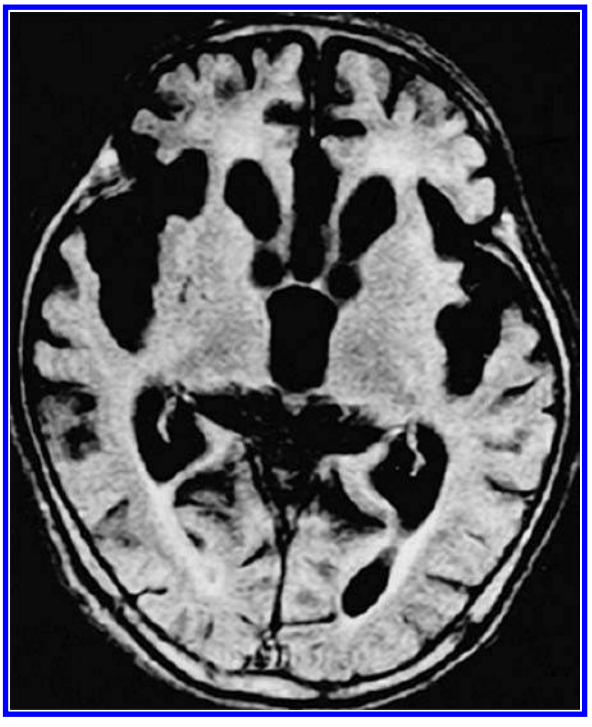

Fig. 10.5 Global brain atrophy, most severe in frontal and temporal lobes, with accompanying ventriculomegaly is seen in this FLAIR-weighted transverse MR image of a 62-year-old man with 10 years of progressive frontotemporal dementia and new onset MND. Reproduced with permission from Toyoshima et al.[38]

An early prospective CT and MRI study of 22 patients with ALS documented the sequential (from earliest to latest) appearance of cerebral atrophy in the following hemispheric regions: frontal and anterior temporal lobes, precentral gyrus (primary motor cortex), postcentral gyrus (primary sensory cortex), cingular gyrus, and corpus callosum.[34] The severity of cerebral atrophy did not correlate with disease duration, severity, or presence of dementia, although only three patients were reported to have dementia. However, patients with early respiratory failure and severe ophthalmoplegia were found to develop marked frontotemporal atrophy most rapidly, whereas three patients surviving 10–20 years without ventilator support had no atrophy. Atrophy of the brainstem tegmentum was also obvious in the five patients with prominent ophthalmoplegia.

A subsequent MRI study of clinically non-demented patients with sporadic ALS (n = 11) and PLS (n = 8), compared to 49 healthy

individuals, revealed significant atrophy of cortex (premotor, primary motor, supplementary motor), and related white matter regions, only in the PLS group.[39] While patients with ALS had prominent reduction in frontal subcortical white matter, cortical surface area was the same as in the controls. This was believed to represent degeneration of axons projecting to the frontal cortex from elsewhere consistent with subtle frontal lobe dysfunction (word fluency, judgment and attention problems), which can occur in ALS. In contrast, a study of 12 nondemented patients with ALS (7 definite and 5 probable by El Escorial criteria) revealed atrophy of the precentral gyrus in all except one with probable ALS.[13]

In a preliminary report of one male with ALS (UMN findings unspecified), serial 3-D morphometric (gradient echo spoiled gradient inversion recovery weighted T1) imaging detected volume reduction in the CST of 44% in the medulla and 37% in the pons.[40] Imaging was performed on the patient on two occasions during a 14-month period when his motor function declined to the point of requiring a wheelchair. In this study, location of the CST fibers was identified by diffusion tensor imaging (DTI), which is described later in the chapter.

MRI changes in PLS have been found in other studies to be primarily cortical atrophy rather than CST hyperintensity,[15,16] although the latter also occurs.[15,41] Imaging in nine patients with PLS revealed 'conspicuous' atrophy in the cortical and subcortical portions of the precentral (frontal) regions.[16] This was seen most clearly in T1-weighted parasagittal images with reduction to approximately 75% of normal. Of note, there was also prominent atrophy in all patients of the parieto-occipital area.[16] Another study of 39 patients with MND, which included 8 with PLS, found cortical atrophy in 29 (74%). Sixteen (41%) of these patients had atrophy restricted to the parietal region (including the superior temporal gyrus), and the majority of these (n = 14) had ALS. In contrast, atrophy of the central region (with or without parietal atrophy) was observed in eight patients, five of them with PLS (63%).[15] Of interest, central atrophy occurred more frequently in PLS than did hyperintensity of the CST. Degeneration of the parietospinal tract was implicated as the cause of parietal atrophy, although there was no explanation for the regional atrophy differences in ALS versus PLS. In a case report, serial MRI of a patient with PLS over an 8.5-year period revealed brain atrophy that progressed from the pericentral and premotor cortices to include the superior parietal cortex and more extensive portions of the premotor and prefrontal cortices[42] (Fig. 10.6).

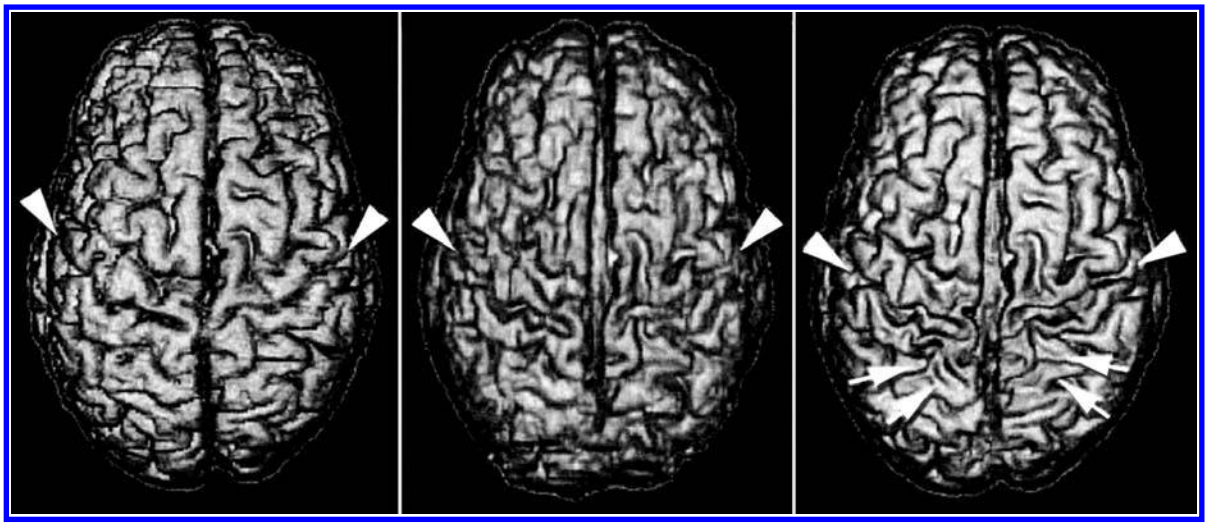

Fig. 10.6 Cortical surface renderings from three-dimensional MRI of a patient with PLS at baseline (left), ~5 years (center), and 8.5 years (right) later. There is progressive atrophy in the paracentral cortex (arrowheads indicate the central sulcus) until it is apparent in the superior parietal region in the most recent scan (double arrows). Adapted from Smith.[42]

A case report of four patients with long-standing juvenile familial ALS (mean duration = 27 years) and overt dementia, demonstrated moderately severe atrophy of the cerebrum and brainstem in one patient undergoing MRI (symptomatic for 21 years).[31] A planimetric MRI study of 74 consecutive patients with sporadic ALS revealed significant cerebral atrophy in the subgroup with neuropsychologic impairment ($n = 45$) compared with the subgroup with intact short-term memory and normal frontal lobe function.[30] Another study of 26 patients with ALS documented frontal atrophy only in the subgroup ($n = 14$) with cognitive impairment.[32] Therefore, pooling ALS patients with and without neuropsychologic impairment may account for conflicting results in other earlier studies of cerebral atrophy.

The corpus callosum has also been found on parasagittal MRI to be atrophic in some types of ALS, particularly when associated with dementia. Of 25 right-handed patients with ALS and 25 age- and sex-matched right-handed control subjects that consecutively underwent T1-weighted MRI, 5 patients had severe atrophy of the anterior fourth of the corpus callosum. Only these patients had cognitive decline and psychiatric symptoms.[33] A patient with PLS was found over an 8.5-year follow-up to have progressive thinning of his corpus callosum, especially in the posterior portion of the midbody, whereas genu, rostrum and splenium were spared.[42] This is the region where post-mortem studies in ALS revealed degeneration of fiber bundles,[37] which are probably homotopic fiber connections between the precentral gyri.

Automated volumetric analysis of cerebral gray and white matter in 16 patients with ALS and 8 normal controls has revealed focal atrophy in the premotor (Brodman areas 8, 9, and 10) but not motor cortex of patients.[35] Despite the lack of cortical atrophy in the precentral gyrus, the underlying white matter along the corticospinal tract (CST) was atrophic in patients with bulbar- but not limb-onset ALS. Neuropsychometric testing of these patients was not performed. This suggested that axonal degeneration occurs as a 'dying back' process, at least in some patients with bulbar-onset ALS.[35] More recently, voxel-based morphometry (VBM) was used on 3-D MRI of 22 patients with definite ALS who had no signs of FTD and 22 age-matched healthy volunteers to assess global and regional white and gray matter volumes.[43] Global brain atrophy was detected in the patients as well as regional reductions of gray matter density in the right primary motor cortex and left medial frontal gyrus. White matter was also reduced in density along both corticospinal tracts, the corpus callosum, cerebellum, frontal and occipital sub-cortical regions.[43]

Three-dimensional volumetric T1-weighted (spoiled fast gradient echo) MRI was performed on 20 patients with ALS who underwent careful neuropsychological evaluation and on 22 normal control subjects.[44] All patients were found by VBM to have atrophy of gray matter involving bilateral motor/premotor cortices, left middle and inferior frontal gyri, anterior portion of the superior frontal gyri, superior temporal gyri, temporal poles and left posterior thalamus, when compared with controls. However, in the 10 patients who met Neary criteria for fronto-temporal lobar dementia (FTLD),[45] most of the frontal regions were significantly more atrophied than in the cognitively normal patients, especially in the left middle and inferior frontal gyri and the medial premotor cortex. No significant differences were found in white matter volumes. Furthermore, no brain regions were more atrophic in ALS patients without cognitive impairment than in those with FTLD. The results were interpreted as supporting the idea that ALS and FTLD comprise a clinical and anatomic continuum.[44]

In contrast, another study with 2-D dual-echo fast spin echo MRI followed by automated voxel-based analysis, found reductions in white matter (but not gray matter) volumes in ALS patients who had frontal lobe cognitive impairment ($n = 11$) and in those who were cognitively intact ($n = 12$), compared with 12 healthy age-matched controls.[46] The most significant reductions of white matter volumes were found in the motor tracts and regions anterior and posterior to the motor pathways of cognitively impaired ALS patients ($p < 0.002$), although cognitively intact patients also demonstrated white matter changes in extramotor cerebral regions ($p < 0.002$). Correlations were observed

between the extent of volume loss and performance impairment, including the Paired Associate Learning and Letter Span Test. Interestingly, no significant differences were detected in white matter volume between cognitively impaired and cognitively intact ALS patients, although gray matter volume was reduced in the cerebellum, brainstem, and parahippocampal gyrus of cognitively impaired patients. However, in view of the white matter abnormalities in extramotor regions of patients with no cognitive change, the authors suggest that their findings support the hypothesis of a continuum of extramotor cerebral and cognitive change in ALS.[46]

A 60-year-old male seen in our clinic with limb-onset ALS and progressive cognitive decline was found to have prominent temporal lobe atrophy on MRI at a time when neuropsychometric testing revealed FTD (Fig. 10.7).

UNCONVENTIONAL MAGNETIC RESONANCE SEQUENCES IN ALS

A number of MR-based modalities are being explored as imaging techniques to study the UMNs of patients with ALS, although experience with them is limited. These include diffusion-weighted imaging (DWI) or diffusion tensor imaging (DTI), functional MRI (fMRI), and magnetization transfer imaging (MTI). Because there is no readily available objective test of UMN dysfunction in ALS – in contrast to electromyography (EMG), which reveals the LMN involvement – a clinically accessible and sensitive MR technique to detect cortical and CST abnormalities would be very useful. All the aforementioned imaging techniques are possible on clinically available 1.5 T magnets, although resolution and acquisition times can be improved on higher field strength magnets (e.g. 3 T). There is much to be learned about how useful each of these modalities will be in assisting with diagnosis and furthering our understanding of ALS. Because only an abbreviated introduction is given here for each of these methodologies, the interested reader is referred to specific articles dealing with the techniques for details.

Diffusion-weighted imaging

Diffusion-weighted imaging (DWI) is based on visualizing the random movement of water molecules in and among various tissue components in health and in disease.[47] The extent of such movement, or diffusion coefficient, is restricted by normal tissue structures, such as neurons, neuroglia, and axons. The apparent diffusion coefficient (ADC), is the quantitative measure of diffusion in a single direction. The presence or absence of directionality influences the ADC because water molecules prefer to move along the direction of structured material (e.g. axon fibers) rather than across it. This directionality of diffusion can be quantified by

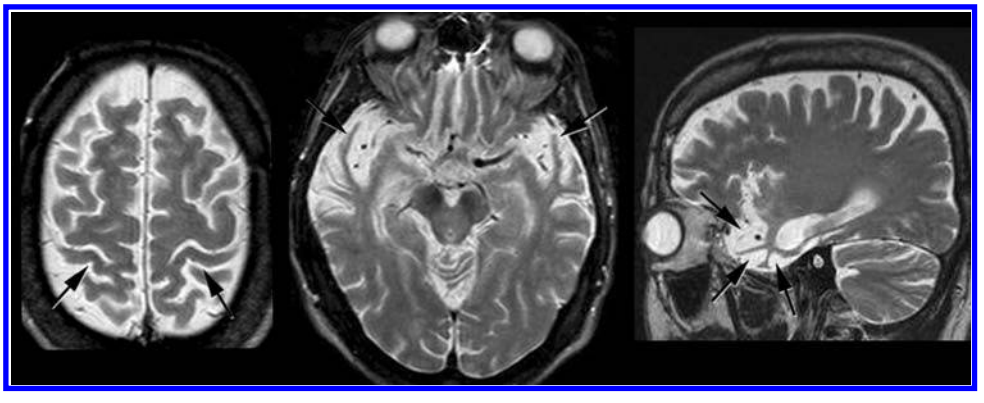

Fig. 10.7 T2-weighted MRI from a 60-year-old patient with ALS and frontotemporal dementia manifest by lack of insight and unusual behavior shows pronounced atrophy of both temporal lobes and only minimal atrophy of other brain regions, including the pericentral area.

an anisotropy value, which is the ratio of diffusivity parallel to vs perpendicular to the fibers. For example, axon fibers result in ADC values that are higher along their length and less across it with correspondingly high diffusion anisotropy. In contrast, areas with little or no directionality (e.g. cortex), result in low ADC values and low diffusion anisotropy. Therefore, various pathologies (e.g. edema, demyelination, wallerian degeneration) can alter the ADC and anisotropy, resulting in regional changes in image appearance.

In a study of 18 patients with ALS and 20 healthy controls and 25 neurologic controls (strokes), no differences were noted in the ADC perpendicular to the CST in the posterior limb of the internal capsule. However, in five patients who had discrete paraventricular lesions, ADC of this region was increased in all directions and anisotropy was therefore lost. This suggested that the pathology in the paraventricular region was different from that in the internal capsule.[48]

DWI in a 58-year-old woman when she had been experiencing progressive gait slowing over 4 months revealed symmetric hyperintensity along the CST which was not evident on the complementary FLAIR sequences, suggesting acute or subacute rather than chronic pathology. One month later, she developed prominent UMN signs and widespread fasciculations on EMG and was diagnosed with ALS.[49]

Diffusion tensor imaging (DTI)

Although useful, a single ADC does not represent what occurs in a 3-D biologic situation where diffusion occurs in multiple directions. The development of rapid echo planar imaging (EPI) made it possible to acquire images with a range of diffusion weighting in multiple directions (diffusion tensor imaging, DTI) within a practical time frame.[50] It allows directionally independent diffusion measures (mean diffusivity, DM) and determination of the anisotropy of diffusion, i.e. the directional dependence. Fractional anisotropy (FA) is the degree of directionality of diffusion within a single voxel and its reduced value indicates that there has been a breakdown of barriers that restrict the free motion of water. On a microscopic scale, axonal membranes are the most important determinant of anisotropic diffusion in neural tissues, although the myelin coating of the axons also has a smaller moderating effect on anisotropy.[51] For example, DM will be high in a less restricted environment (e.g. cortex) and low in a more restricted environment (e.g. white matter tracts). Alternatively, FA will be high in a restricted environment (e.g. intact white matter tracts) and low in a less restricted environment (e.g. disrupted or degenerating white matter tracts). Images can be generated representative of these variations, allowing localization and visualization of myelinated fiber tracts (tractography). Tractography uses diffusion tensor data to trace white matter pathways *in vivo* within the brain. Several DTI studies of patients with ALS have been published recently, the majority utilizing 1.5 T magnets and diffusion weighting in six directions, unless otherwise indicated. This technique is only beginning to be used to study ALS patients with FTLD.

The first DTI study in ALS examined 22 patients (11 limb-onset and 11 bulbar-onset) compared with 20 healthy, age-matched controls.[52] Coronal images centered to include the posterior limb of the internal capsule revealed significantly increased mean diffusivity along the CSTs of patients compared with controls. FA was reduced along the CST of all patients and correlated with measures of disease severity ($r = 0.63$, $p = 0.003$) and UMN involvement ($r = -0.55$, $p \leq 0.01$). This was due to significant reductions in bulbar-onset and not in limb-onset ALS patients. Of interest, none of the patients with both increased diffusivity and reduced anisotropy had CST hyperintensities. However, there was significant overlap between patient and control values, suggesting that the technique may not be useful for early diagnosis of individual patients. Longitudinal studies of mean diffusivity and fraction anisotropy in patients are required to determine the usefulness of DTI in studying disease course and drug response in ALS.

In a small study of three patients with different principal symptoms of ALS, i.e. each with either upper motor neuron (UMN)-predominant, lower motor neuron (LMN)-predominant or bulbar features, serial DTI of the pyramidal tract was

performed on a 2T magnet over a 9-month period. Progressive loss of diffusion anisotropy (–14%) occurred in the pyramidal tract of the patient with UMN involvement, but not of the others, which paralleled a reduction of the ALS Functional Rating Scale (ALSFRS)[53] (Fig. 10.8). This was the first study to demonstrate that DTI could detect progressive degeneration of the CST in a patient with known clinical UMN dysfunction. However, the authors correctly indicated that larger numbers of patients with different varieties of disease would need to be studied to determine whether DTI would be useful in assessing disease progression in therapeutic trials.[53]

DTI was performed in 21 patients (16 men, 5 women) with probable or definite ALS and 14 normal controls (9 men, 5 women) at multiple levels along the CST between the internal capsule and pyramids in the medulla in 7 noncollinear directions.[54] All patients except two had either prominent UMN or mixed UMN and LMN signs. Regions of interest (ROIs) were manually placed onto the CST with the assistance of co-registered z directional ADC maps to exclude nonpyramidal fibers tracking in orthogonal directions. Mixed model regression analysis revealed that FA had a downward linear trend from the cerebral peduncles to the pyramids and was significantly lower in the ALS group than controls at multiple levels of the corticospinal tract. In addition, FA at the internal capsules was found to be higher on the right in patients and controls. MD also demonstrated a similar although upward change moving from the internal capsules to the pyramids. However, significant differences between groups were detected only at the internal capsule level, possibly because of high between-subject variability at brainstem levels. No correlations were observed between the ALSFRS or an index of disease rate and the diffusion indices. The authors concluded that the differences in diffusion characteristics along the rostrocaudal extent of the CST likely represented the distribution of pathological damage in ALS. However, they discussed that technical limitations of the ROI technique and inherent differences in underlying tract architecture could also influence the results.

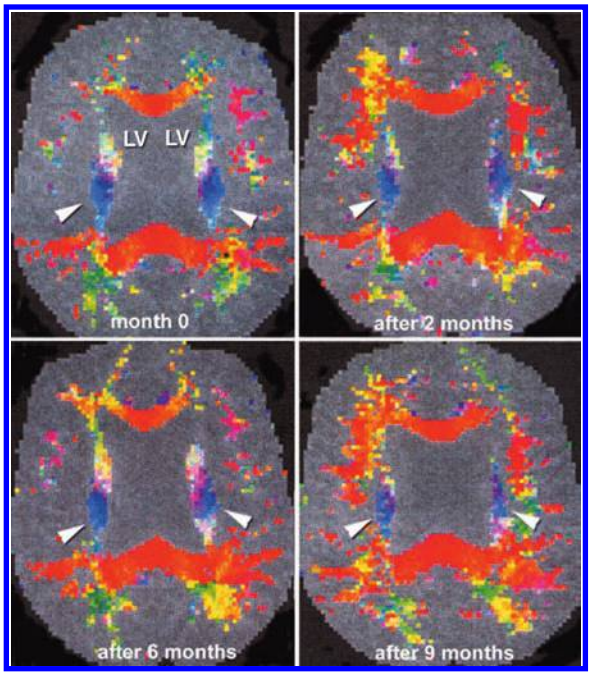

Fig. 10.8 Sequentially obtained diffusion tensor imaging (DTI) in a patient with ALS over a 9-month period reveals progressive loss of fractional anisotropy (FA) in the corticospinal tract (CST) at the level of the mid lateral ventricles (LV), represented as a diminishing region of blue pseudocolor (arrowheads). Adapted from Figure 2 of Jacob et al.[53] with kind permission of Springer Science and Business Media.

In a more recent DTI study of 7 patients with probable ALS (4 women, 3 men) and 11 age- and sex-matched healthy volunteers, diffusion tensor data were used to generate diffusion tensor tractography (DTT) to more accurately localize the supratentorial CST.[55] Subsequent voxel-based diffusion tensor analysis performed along the CST revealed significantly decreased FA in the subgyral white matter of patients in the left ($p < 0.042$) but especially in the right ($p < 0.0070$) precentral frontal regions. However, no differences in FA were detected outside the CST or along its caudal extent into the brainstem. Despite this inconsistency, this study was the first to employ DTT for voxel-based diffusion tensor analysis demonstrating supratentorial CST abnormalities in patients with ALS.[55]

High angular resolution DTI (HARD) was compared with routine MRI and neurologic

assessment in its ability to detect UMN pathology in 25 ALS patients with definite UMN signs compared to 23 healthy volunteers and 4 patients with isolated LMN signs.[56] Compared to the 6 direction diffusion-weighted acquisitions in standard DTI, HARD acquisitions in this study were obtained from 54 distinct, spatially isotropically arranged, diffusion-weighted gradient directions. Hyperintensity of CST in the corona radiate on proton density-weighted images and motor cortex hypointensity on T2-weighted images distinguished patients with UMN involvement from patients with 100% specificity but with only 20% sensitivity. FA (but not MD) was reduced in the posterior limb of the internal capsule in ALS patients compared with volunteers ($p < 0.01$). This reduction was 71% specific when its threshold value had a sensitivity of 95% to detect patients with ALS, including those with isolated LMN signs. Although HARD was more sensitive than conventional MRI or neurologic assessment in detecting UMN pathology, the authors concluded that it lacks the specificity required of a diagnostic marker of ALS. Rather, it may have a role as a quantitative tool for monitoring progression of UMN pathology.[56]

DTI with a 3.0 T MR system used 25 non-collinear diffusion gradient directions to examine water diffusion changes along pyramidal tracts of the brainstem in 16 patients with ALS and 11 healthy, age- and sex-matched controls.[57] Multifactorial ANOVA revealed that FA and MD were both significantly different between the two groups and for anatomical level ($p < 0.001$) studied. However, analysis for each anatomical level revealed that only the cerebral peduncle showed significant differences of diffusion properties between patients and controls ($p < 0.001$ for FA, $p = 0.001$ for MD). This may have been due, in part, to the consistency of FA values at the level of the midbrain but great variability in FA and MD between contiguous slices in the pons and medulla. Similar to an earlier DTI study of the supratentorial CST,[52] the FA value and extent of UMN signs were inversely related on correlation analysis ($r = -0.81$, $p < 0.001$). Therefore, the authors suggested that altered diffusion properties in the cerebral peduncle of patients with ALS may be a true reflection of pathological changes in structures rather than regional architectural variations of the corticospinal tracts or experimental artifacts.[57]

DTI has been used to elucidate if pathogenesis of ALS results from anterograde or retrograde axonal degeneration by measuring ADC and FA along the CST at corona radiata, internal capsule and pontine levels in 8 ALS patients with clinical upper motor neuron signs and 11 healthy age-matched controls.[58] Compared with controls, patients had significantly higher ADC ($p = 0.04$) and lower FA ($p = 0.01$) at the three CST levels overall. However, significant changes at each level were detected only at the internal capsule for ADC and only at the pons for FA. Only a trend to increased ADC in the pons and decreased FA in the internal capsule was detected, with no differences in the corona radiata for either parameter. This apparent gradient-like variation along the CST of ADC and FA values was interpreted by the authors to support the 'dying back' hypothesis of neurodegeneration in ALS.[58]

Nine ALS patients with some degree of UMN and LMN involvement and 6 patients with only LMN signs at the time of DTI all had significantly decreased FA in the CST compared with 12 healthy age-matched controls.[59] This occurred primarily in the CST at the level of the internal capsule (right, $p < 0.00001$; left, $p < 0.012$) but also in the corona radiata beneath the motor and premotor cortices as well as in the brainstem. Interestingly, significant reductions of FA in all patients were also detected in the corpus callosum and thalamus ($p < 0.01$), which is consistent with previously reported involvement of these structures in ALS. All patients with no UMN signs at the time of DTI eventually developed them, although a time-frame is not indicated. The authors concluded that DTI can detect UMN involvement in ALS patients before this is clinically apparent and may therefore contribute to earlier diagnosis of ALS.[59]

ROI using diffusion tensor tractography (DTT) was performed on 16 patients with ALS (9 limb-onset, 7 bulbar-onset) patients and 9 age-matched healthy volunteers.[60] FA was measured in ROIs after semi-automatic placement on the tracts, which were defined by DTT methods. Not only were mean FA values lower in all ALS

patients compared with controls, but bulbar-onset patients had significantly lower values than did limb-onset patients, indicating more fiber tract disruption (degeneration) in the former group.[60]

DTI was used to demonstrate the presence of CST abnormality as revealed by increased MD and reduced FA in 18 patients with ALS but not in 8 male patients with progressive muscular atrophy (PMA), all compared to 12 control subjects (all age-matched).[61] Correlations were also noted in ALS patients between MD and disease duration, FA and disease severity. Overall the findings confirm what is known clinically: that the CST is abnormal in patients with UMN signs (ALS) but not in those without UMN findings (PMA patients). However, because the lack of UMN signs clinically may not be reflective of the underlying pathology, future studies comparing DTI data with post-mortem analysis for tissue evidence of CST degeneration will be necessary to assess the true sensitivity of this imaging modality.

Magnetization transfer imaging

Cross-relaxation between free ('mobile') water protons and restricted protons in macromolecules is the basis of magnetization transfer imaging (MTI). This technique serves to enhance contrast or itself provide a novel contrast mechanism which allows quantification of structural or biochemical changes in certain pathologic states (for review see Finelli[62]). MTI shows significant promise in the study of central nervous system lesions in multiple sclerosis but its use in ALS has been very limited.

Magnetization transfer (MT) measurements were performed in the brains of patients with ALS (n = 9) and control subjects (n = 9).[63] MT ratios (MTRs) of a 3 mm diameter circular region were obtained from the posterior third of the posterior limb of the internal capsule (location of CST) as well as widespread gray and white matter areas. Only the region of the CST in the posterior limb of the internal capsule revealed MTR values 20% lower in patients than in controls ($p < 0.0007$). This decrease was proposed to represent degeneration of the CST. Of note, all patients had MTRs below the normal mean, although only three (33%) had T2-weighted CST hyperintensity in this location. This suggests that MTI may be able to detect earlier stages of CST degeneration. However, no relationships were observed between MTR and ALS scores, duration of illness, or signal intensity on T2-weighted images.

In contrast, a subsequent study found MTR to be reduced by only 2.6% in CST- but not in non-CST-related white matter of 10 ALS patients compared with 17 age-matched controls.[64] This mean difference was statistically significant ($p < 0.02$) because of the small variance, even though the difference was small. However, individual MTR values of patients (8/10) and controls (15/17) overlapped extensively in the same 95% confidence interval, indicating limited usefulness for diagnosis. There was a significant correlation with UMN dysfunction (r = 00.61, $p < 0.005$), as revealed by maximum rate of finger and foot tapping.[64]

A qualitative MTR technique known as T1-weighted spin-echo (SE)/magnetization transfer contrast-enhanced (MTC) imaging and FLAIR-weighted sequences were performed at 1 T to study the CST of 25 patients with ALS (14 men, 11 women) and 21 age- and sex-matched healthy subjects.[65] All but one patient had combined UMN and LMN signs (El Escorial definite n = 22, probable n = 2, suspected n = 1). In control subjects, the CST appeared hypointense along its extent, whereas in 80% of the ALS patients it appeared hyperintense ($p < 0.05$); none of the control subjects showed hyperintensity. CSTs in FLAIR images, in contrast, were hyperintense in both groups with no significant difference. In the authors' hands, this technique allowed 100% separation between patients with ALS and controls, at least in the 80% of patients with CST hyperintensity on T1-weighted SE MTC imaging.[65]

Functional imaging

Activation of cortical neurons results in increased regional blood flow, which in turn results in a relative decrease of blood deoxyhemoglobin locally. This occurs because the increased blood flow is not matched by increased oxygen extraction. Because deoxyhemoglobin is paramagnetic,

differences in the magnetic field characteristics of it and oxyhemoglobin at activated areas results in increased signal intensity on functional MRI (fMRI) (for review see Ogawa et al.[66]).

The first fMRI study in patients with ALS utilizing standard motor paradigms (e.g. index–thumb opposition) found activation of cortical regions outside the normal primary motor area, including bilateral supplementary motor areas (SMAs), premotor, and sensory cortices.[67] This expanded somatopic representation is similar to what has been reported in earlier PET studies of patients with ALS (see below) and was especially enlarged when upper motor neuron signs were prominent. It is unclear whether this increased 'output zone' is due to loss of inhibitory cortical interneurons or inhibitory pyramidal cell axon collaterals, or whether it represents the recruitment of motor neurons in less affected regions that compensate for dysfunctional ones in degenerating areas. However, an unexpected observation was the alteration of cortical activation following sensory stimulation of the hand and foot of patients with ALS compared with controls. Mechanical stimulation of the hand (palm) or foot (sole), as in a Babinski response, resulted in diminished activation of sensorimotor cortex.[67] This suggests somatosensory dysfunction at the CNS level, which could explain the not uncommon sensory complaints of patients with ALS who have normal peripheral sensory nerve function. Depending on the reproducibility of these findings, the combination of cortical activation that is increased with motor paradigms and decreased with sensory stimulation may provide a marker of cortical dysfunction in ALS. However, it is unknown whether these changes occur early enough that they may be diagnostic markers. Neither is it known if such changes could be used as surrogates for neuronal recovery in therapeutic trials.

Cortical reorganization was examined in 11 patients with ALS compared with 13 healthy volunteers who used a simple hand grip force transducer to squeeze at 10% of their own maximum voluntary contraction force.[68] Cluster analysis of fMRI data was performed after transformation of anatomical and functional images into standardized (Talaraich) space. Patients demonstrated activation of motor cortex more anteriorly than controls, including the premotor area and an enhancement of SMA activation with a shift toward the pre-SMA. The results were interpreted as indicating recruitment of related motor areas usually involved in planning and initiation of movement when primary motor areas degenerate.

RADIOLABELED TRACER IMAGING

Positron-emission tomography (PET) and single-photon emission computed tomography (SPECT) are nuclear medicine techniques that have been used to assess cerebral blood flow (CBF) and neuronal metabolism in various disease states, including ALS[69,70] (for additional references see Del Sole et al.[71]). Patients with MND, particularly ALS, have decreased CBF, and diminished neuronal metabolism, primarily in sensorimotor regions. CBF abnormalities in extramotor regions have also been detected by PET and SPECT in some ALS patients with clinical or subclinical dementia. The use of newer radiolabeled tracers that identify specific neuronal or glial populations may provide unique insights into MND degeneration and even pathogenesis. Although these nuclear medicine techniques have been used primarily for research purposes, they may assist in the clinical diagnosis of MND, especially with the development of specific tracers and in cases associated with dementia.

PET

Results from PET studies in ALS patients have been somewhat inconsistent, at least in part because of differences in technique and analysis of statistical data.[69,70,72–75] Various radiolabeled isotopes have been utilized: [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) and 6-fluorodopa (^{18}F-Dopa) for measurements while the subject is at rest, and oxygen 15 gas (^{15}O) or oxygen 15-labeled carbon dioxide ($C^{15}O_2$) primarily for studies while the subject performs certain motor tasks. The latter studies have provided information on the dynamic state of brain activation in ALS and revealed abnormalities when measurements at rest were normal. More recently, ligands targeting neuronal receptors

have been used in an attempt to document cell loss or other changes expected in ALS.

PET studies at rest

In general, nondemented patients with ALS at rest appear to have at least a trend toward diminished brain glucose metabolism in the sensorimotor cortex and basal ganglia.[69] Patients who are demented or have neuropsychologic impairment reflective of frontal lobe dysfunction have more significant FDG hypometabolism in frontal (superior and inferior) and temporal (superior and mesial) cortical regions.[76] This is demonstrated in the 60-year-old male with ALS and FTD discussed above who was found on routine MRI to have prominent temporal lobe atrophy (Fig. 10.9). Anatomic localization of the hypometabolism is facilitated by co-registering the PET and MRI images from the same individual (Fig. 10.10). The regional distribution of hypometabolism in ALS patients with dementia is opposite that of patients with Alzheimer's dementia (low in parietal cortex and normal in frontal lobes). 6-Fluorodopa PET studies have been performed in patients with sporadic ALS because of the association of ALS with parkinsonism (e.g. Guamanian ALS).[74] Compared with age-matched controls, striatal 6-fluorodopa uptake progressively decreased as the ALS progressed.

PET studies with activation

Results of PET studies using ^{15}O and $C^{15}O_2$ to measure regional CBF (rCBF) and oxygen metabolic rate in patients with ALS making freely selected joystick movements suggested cortical reorganization and abnormal recruitment of nonprimary motor areas as a result of motor neuron loss.[72] Stereotyped movements in ALS patients revealed impaired activation in frontal lobe regions, suggesting underlying frontal lobe cognitive deficits even though none were clinically demented. Similar activation PET studies of five patients with LMN-predominant ALS have uncovered cortical dysfunction (anterior insular cortex) even when no abnormalities were detectable at rest.[73] Abnormal activation of this perisylvian area was thought to reflect recruitment of an accessory sensorimotor area in response to limb weakness. Verbal fluency and testing of executive frontal lobe function have identified other extramotor neuronal deficits, especially along a thalamofrontal association pathway in some patients with ALS.[75]

Novel PET tracers

Novel radiolabeled ligands are beginning to be used in ALS in an attempt to identify changes in number or functioning of motor neurons and neuroglia. The $GABA_A$ ligand ^{11}C-flumazenil (^{11}C-FMZ) binds to GABA receptors localized to cortical pyramidal neurons. A study of 17 nondemented patients with definite or probable ALS and 17 controls found significantly reduced ($p < 0.001$) FMZ volumes of distribution (which correlate closely with receptor density) in several motor and extramotor cortical regions.[77] These include prefrontal, premotor, motor,

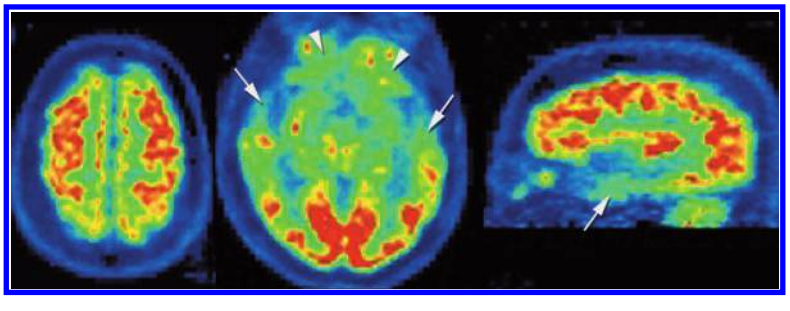

Fig. 10.9 [^{18}F]2-fluoro-2-deoxy-D-glucose PET brain imaging of the 60-year-old patient discussed in Fig. 10.7, showing reduced metabolism in both temporal lobes (arrows) and inferior frontal lobes (arrowheads) but not in the superior frontal regions.

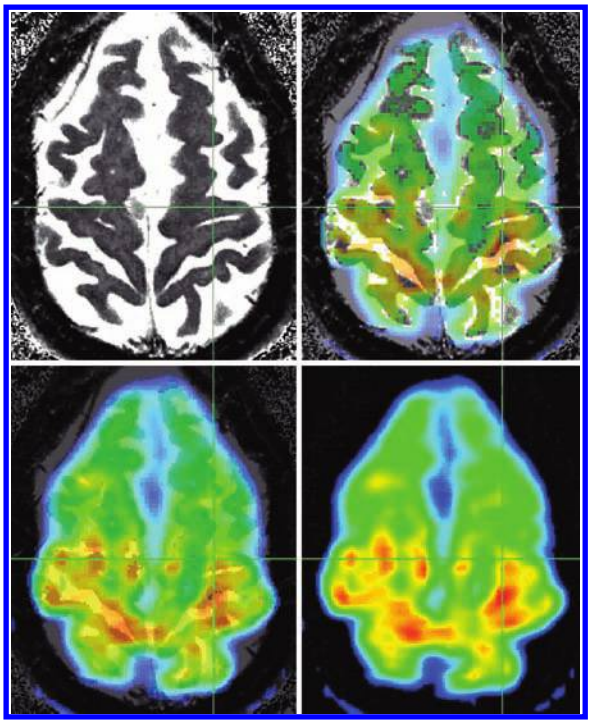

Fig. 10.10 Co-registration of transverse PET and MR images from a 53-year-old man with ALS and frontotemporal dementia reveals markedly diminished metabolism of [^{18}F]2-fluoro-2-deoxy-D-glucose in motor and premotor regions as well as cortical atrophy. Blending of the superimposed images from MRI only (upper left) to PET only (lower right), allows localization of hypometabolism to frontal regions, especially the superior frontal gyri and parasagittal portions of the precentral gyri. Crossing of planar lines indicates the anterior portion of the left precentral gyrus (primary motor cortex). Reproduced from Jacob et al.[53]

parietal, and visual association cortices ($p < 0.001$) and relative reductions in other regions, including Broca's area, the right temporal cortex.

The 5-hydroxytryptamine (5-HT) PET ligand specific for 1A receptors (5-HT$_{1A}$), ^{11}C-WAY100635, binds to the axon hillock of motor neurons in cortex (pyramidal), brainstem and spinal cord.[78] A preliminary study found approximately 39% (range 33–57%, $p < 0.0001$) less global cerebral binding of ^{11}C-WAY100635 in ALS pateints ($n = 6$) than in healthy, age-matched controls ($n = 8$).[79] There was no regional cortical variation or correlation between loss of binding and disability. This preliminary study was unable to determine whether the loss of binding represents a down-regulation of 5-HT1A receptors, or loss of the neurons containing them.

Microglia become activated and hypertrophic as neurons and axons degenerate and have been implicated in the propagation of the degeneration. The PET ligand ^{11}C-PK11195 binds to peripheral benzodiazepine receptors and reportedly identifies activated microglia, as has been demonstrated in Alzheimer's disease even early in the course of disease.[80] Therefore, it may be a useful marker for cortical and subcortical degeneration in ALS, possibly in early disease.

SPECT

Unlike PET studies, SPECT studies do not measure CBF, although values in ALS are usually expressed relative to blood flow in regions not believed to be affected, such as the cerebellum[32] (for additional references see Van Zandijcke and Casselman[9]). The potential clinical usefulness of SPECT over PET arises from several differences: more widely available machines and familiarity of technique, less complex technical support, less expensive and more stable radiochemicals (^{123}I-iodoamphetamine, IMP; [^{99m}Tc]-*d,l*-hexamethyl-propylene-amine-oxime, HMPAO; ^{123}I-N-[3-iodopropen-2-yl]-2β-carbomethoxy-3β[4-chlorophenyl]-tropane, IPT).

The majority of studies have revealed regional cerebral hypoperfusion in motor and premotor areas of many patients with ALS. Those with superimposed dementia have more widespread hypoperfusion, including regions anterior and often inferior to the primary motor cortex. As with PET studies at rest, SPECT abnormalities were not found in patients with LMN-predominant ALS. A pilot radioligand study examined whether patients with ALS and no signs of parkinsonism have presynaptic nigrostriatal dopaminergic deficits detectable by SPECT. Using the cocaine analog ^{123}I- IPT, which selectively binds to the dopamine transporter located on dopaminergic nerve terminals, striatal IPT binding was found to be significantly

reduced ($p < 0.01$) in the ALS group ($n = 18$) compared with age-matched controls ($n = 11$).[81] Striatal IPT uptake values overlapped between groups with 12/18 patients having values > 1 SD below the control mean. There was no correlation between uptake values and site of disease onset, age of patient, or duration of the disease. These data suggest that nigrostriatal dopaminergic neurons are subclinically affected in a subset of patients with sporadic ALS.

PROTON MAGNETIC RESONANCE SPECTROSCOPY IN ALS

^{1}H-MRS allows noninvasive *in vivo* measurement of certain proton-containing, nonwater metabolites, which may be altered in various diseases (for review see Lin et al.[82]). Of these metabolites, *N*-acetyl (NA) groups, e.g. *N*-acetylaspartate (NAA) and *N*-acetylaspartylglutamate (NAAG) are the most easily detected and are found only in neurons, at least in the mature CNS. In the cerebrum, most of the NA groups are composed of NAA while in the brainstem, the proportion of NAAG increases. Therefore, NAA has been used as a surrogate marker of neuronal (including axonal and dendritic) health, at least in the cerebrum. Two other easily identified metabolites in the CNS are choline (Cho), a lipid component in cell membranes which does not appear to be significantly altered in ALS,[83–87] at least in the cortex,[88] and creatine-phosphocreatine (Cr), compounds involved in energy metabolism with a relatively even distribution in the brain, which have been used to normalize signal from the other metabolites. Therefore, decreased NAA/Cr or NAA/Cho resonance intensity is consistent with neuronal loss or dysfunction, as shown in a patient with UMN-predominant ALS (Fig. 10.11). A stereologic study estimating the total number of neurons in the neocortex and motor cortex of eight patients with ALS and nine controls found no differences between the groups.[89] This suggests that NAA changes in ALS are not simply a reflection of neuronal loss but likely represent neuronal dysfunction or shrinkage.

One of the goals of ^{1}H-MRS in ALS, therefore, has been to assess objectively and quantitatively the existence and degree of UMN dysfunction or degeneration *in vivo*. Most ^{1}H-MRS studies of ALS have utilized a long echo time, usually TE

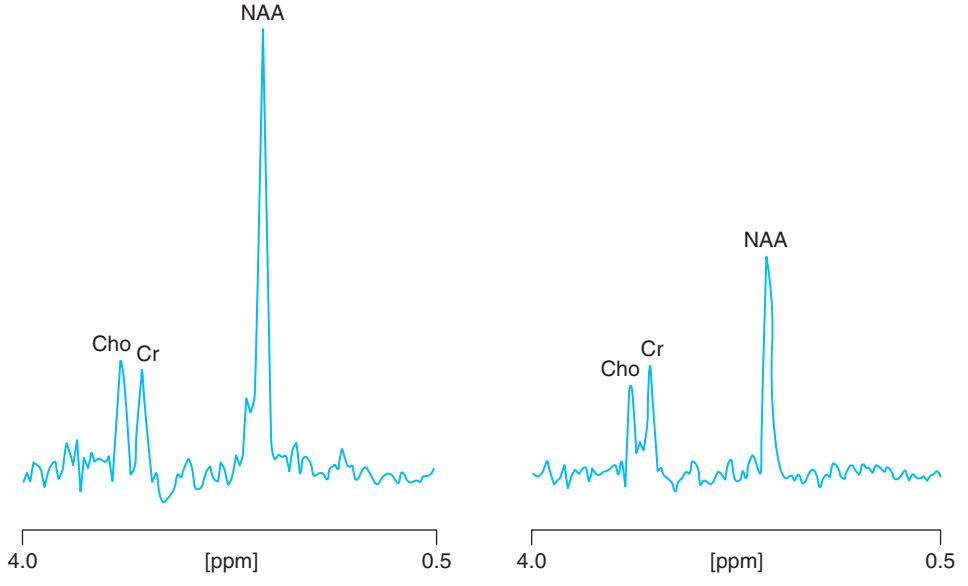

Fig. 10.11 Long TE ^{1}H-MRS of the precentral gyrus (primary motor cortex) shows an *N*-acetylaspartate (NAA) signal that is higher, relative to creatine (Cr), in a healthy age-matched volunteer (left) than in a patient with upper motor neuron (UMN)-predominant ALS (right). Both the Cr and choline (Cho) signal intensities remain relatively constant. ppm, parts per million. Adapted from Pioro et al.[83]

136 ms or TE 272 ms, which reveals three major metabolites normally found in the CNS, i.e. NA groups, Cho, and Cr.[90] Some ALS ^{1}H-MRS studies have employed short TE sequences (e.g. 40 ms or less) because they reveal additional metabolites with short T2 times, including *myo*-inositol (mI), glutamate (Glu) and glutamine (Gln), which are of potential interest in ALS.[84,91–94]

Pericentral neocortex

Patients with MND were first reported to have ^{1}H-MRS evidence of neuronal degeneration or loss in the neocortex and subjacent white matter if clinical LMN changes were accompanied by definite UMN signs (classic ALS) or *p*robable *u*pper *m*otor *n*euron *s*igns (ALS-PUMNS) but not if present in isolation (progressive spinal muscular atrophy, PSMA).[83] Compared with healthy controls, NAA/Cr values from the primary sensorimotor cortex were decreased most significantly in patients with classic ALS, followed by those with ALS-PUMNS (Fig. 10.12). Because long TE spectra were obtained simultaneously from multiple voxels, or volume elements (i.e. proton magnetic resonance spectroscopic imaging, ^{1}H-MRSI), data could be analyzed from multiple cortical regions. A gradient of improving NAA/Cr ratios was detected as distance increased from the pre- and post-central gyri until values were no different from controls in the superior frontal gyrus, anteriorly. This relatively widespread distribution of putative neuronal abnormality is consistent with the extensive cortical origin of the primate CST but also may represent involvement of nonmotor regions. Evidence that decreased NAA/Cr is a marker of UMN pathology (of the corticomotoneuron, at least), included: proportionately lower ratios as severity of UMN signs increases (classic ALS vs ALS-PUMNS) and normal ratios when no UMN signs exist (PSMA); continued decline of NAA/Cr ratios in the primary motor and precentral cortices of a patient with ALS-PUMNS who underwent repeat ^{1}H-MRS after 8 months of clinical deterioration.

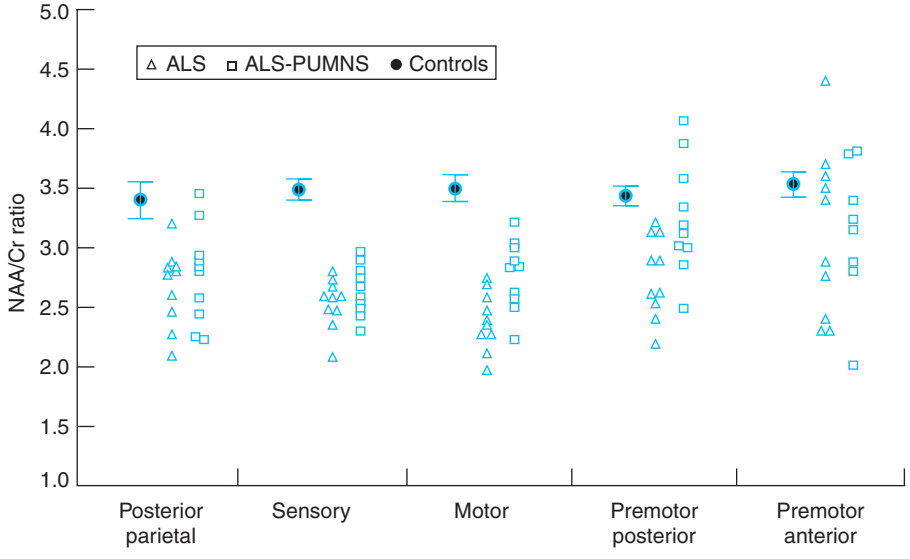

Fig. 10.12 Scatter plot of individual *N*-acetylaspartate/creatine (NAA/Cr) ratios in five cortical regions of patients with classic ALS (triangle, $n = 12$) and with ALS-PUMNS (square, $n = 12$). Compared with the means (± SEM) from healthy age-matched controls ($n = 10$), statistically significant ($p < 0.05$) decreases occur in the primary motor and primary sensory cortices of all patients. NAA/Cr ratios remain significantly lower in the posterior portion of the premotor cortex and posterior parietal cortex of the ALS group only and are in the normal range in more anterior regions. Statistical analysis was by Wilcoxon rank sum test. Data from Pioro et al.[83]

Subsequent ^{1}H-MRS studies – mostly single voxel – of the motor cortex in patients with ALS have confirmed a reduction of NAA signal, relative either to Cr, Cho, Cho+Cr (as a ratio)[84,86,93–101] or to internal water (as relative concentration).[13,87,97,102] ^{1}H-MRS studies published after 1994 have utilized the El Escorial WFN criteria to group patients based on certainty of diagnosis.[103] Most studies have reported concordant results despite differences in hardware (acquisition parameters) and software (post-processing).[90] These would have to be resolved if multicenter clinical trials are to incorporate ^{1}H-MRS as a noninvasive technique to monitor the effects of investigational treatments on cerebral metabolites.

Single voxel ^{1}H-MRS

Long and short TE acquisitions were used in a single voxel ^{1}H-MRS study of the precentral gyrus in 33 patients with MND, as defined by El Escorial criteria[103] and 24 healthy controls.[93] NAA/Cr and NAA/Cho were both significantly lower in patients, especially in the subgroup with definite ALS. Both Cho/Cr and mI/Cr were increased, but only in the latter subgroup. Nine patients who underwent follow-up scans for up to 2 years revealed progressive reduction, primarily in NAA/Cho. This decrease was most dramatic in patients with the most normal ratios on initial investigation, such as one patient initially thought to have a pure LMN syndrome (suspected ALS) but who subsequently developed UMN signs. Because Cho/Cr was found to be elevated in the suspected and especially definite ALS groups, however, the progressive decline in NAA/Cho may not have resulted only from a loss of NAA, *per se*, but also because of increasing Cho signal. Increased Cho/Cr could result from similar causes, as discussed above. A subsequent study using long TE (272 ms) by the same group[97] on 70 patients with ALS compared with 48 healthy control subjects, helped to clarify the initial observations. First, it confirmed the previous findings that NAA/Cho and NAA/Cr ratios were reduced in all El Escorial subgroups ($p < 0.001$) and Cho/Cr ratio was increased in patients with definite ALS ($p < 0.05$). Metabolite ratio changes corresponded to the lateralization of clinical symptoms and were weakly correlated with disease duration and disease severity. In 16 patients with follow-up scanning over a mean (± SD) of 12.1 ± 8.7 months, NAA/Cho dropped by 9.1% ($p < 0.01$), and Cho/Cr increased by 7.0% ($p < 0.01$). These changes of metabolite ratios were significantly correlated with progression of disease severity. Second, when absolute metabolite concentrations were obtained in 30 patients and 15 controls by using the unsuppressed water signal as an internal reference, NAA ($p < 0.001$) and Cr ($p < 0.05$) were reduced in motor cortices of patients, whereas Cho concentrations remained unchanged. The importance of these absolute concentration findings is that NAA/Cr ratios may be underestimating the degree of reduction of NAA since Cr may also be decreasing. Rather, NAA/Cho ratios were suggested as most appropriate to detect motor cortex degeneration by single-volume ^{1}H-MRS.

Another study used short and long TE (STEAM) ^{1}H-MRS and the unsuppressed water signal to measure metabolite concentrations in the precentral gyrus.[13] The mean concentration of NAA was decreased ($p < 0.001$) in 12 patients with definite or probable ALS compared with 10 age-matched healthy control subjects, and Cho or Cr concentrations were unaltered. NAA concentration in primary motor cortex correlated weakly with Norris scale scores ($r = 0.30$; $p < 0.0001$) but not with the ALS Functional Rating Scale score or disease duration. In addition, the patients with hypointense signal in the primary motor cortex ($n = 7$) had lower NAA ($p < 0.009$) than those without ($n = 5$).

A single-volume short TE (20 ms, STEAM) ^{1}H-MRS study determined concentrations of metabolites in the motor cortex of 20 ALS patients and 14 age-matched controls[104] by using the LC model, which fits *in vivo* data with an *in vitro* basis set of reference metabolites.[105] NAA content in ALS patients compared with controls was reduced in the motor cortex by 7.7% ($p = 0.015$). The degree of reduction of NAA was related to the severity of UMN abnormalities. This group used the same techniques to expand their studies of motor and extramotor cortices of 18 patients with ALS and 12 healthy volunteers.[22]

Concentrations for metabolites NA, Cr, Cho, Glu, Gln, and mI were determined in the left precentral and cuneus (occipital) gyri. In addition, T2-weighted signal intensities of the precentral gyrus were assessed qualitatively in a blinded fashion. No difference in metabolite concentrations between groups was observed for the cuneus gyrus. For the precentral gyrus, the ALS group had significantly decreased NA and Glu but increased Cho and mI. The metabolite changes significantly correlated with the severity of clinical UMN signs and were greater in the subset of ALS patients with precentral gyrus signal changes on imaging. In particular, the increased mI concentration was associated with cortical hypointensity on fast spin-echo images.

A single-volume study compared the ability of ^{1}H-MRS and conventional MRI to detect abnormalities of the UMN in 43 patients with MND (ALS, ALS-PUMNS, PLS, LMN-predominant MND) and 14 control subjects.[98] MR images were evaluated blindly for corticospinal tract hyperintensity and dilatation of the central sulcus, an indicator of motor cortex atrophy. Mean ratios of NAA/Cr from right or left motor cortex of control subjects and patients with ALS and PLS were significantly different ($p < 0.05$), and a cut-off value of 2.5 was deemed optimal. By this criterion, NAA/Cr values were abnormal in 79% (15/19) of patients with ALS and ALS-PUMNS, 67% (12/18) of patients with PLS, 17% (1/6) of patients with nonUMN disorders, and 7% (1/14) of control subjects. In contrast, corticospinal tract hyperintensity, central sulcus enlargement, or both, were found in only 43% of the ALS and ALS-PUMNS group, 24% of the PLS group, and 7% of the control group. Using these criteria, the receiver operating characteristic curves illustrated that ^{1}H-MRS of the motor cortex was more sensitive and more specific than standard MR findings in detecting UMN disease (Fig. 10.13).

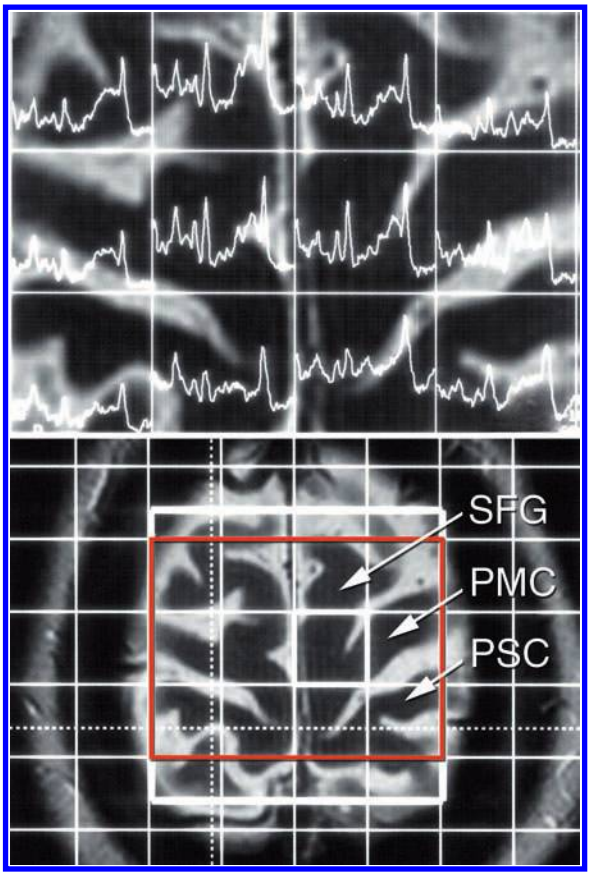

Fig. 10.13 Multi-voxel ^{1}H-MRS in the transverse plane of a patient with ALS (bottom half) shows short TE spectra within individual voxels which are obtained from the neocortex (top half). Signal intensities of metabolites can be calculated from the individual spectra in each voxel overlying specific gyri. The part of the volume of interest outlined in red (bottom) overlies the pericentral region which includes the parasagittal portions of the superior frontal gyrus (SFG), primary motor cortex (PMC), and primary sensory cortex (PSC).

In contrast, another single voxel long TE (136 ms) ^{1}H-MRS study revealed no significant reductions of NAA/Cr or NAA/Cho in the parasagittal primary motor cortex and subcortex of 19 patients with ALS compared to 8 healthy age-matched control subjects.[86] However, the patients with bulbar-onset ALS ($n = 8$) had lower NAA/Cr ratios than those with limb-onset ($n = 8$) disease. This is somewhat curious because placement of the 4 ml volume of interest was in the parasagittal subcortical white matter through which lower extremity- and not bulbar-projecting CST fibers would be expected to traverse. Significant correlations were observed between NAA/Cr reduction and the Hillel ALS Severity Scale[106] ($r = 0.63$, $p = 0.01$) but not the degree of UMN dysfunction, as assessed by a modified Ashworth Spasticity Scale and a reflex

scale (unvalidated) devised by the authors. A follow-up study by the same authors[102] examined the absolute concentrations of NAA, Cr, and Cho in the subcortical white matter of the motor region in 16 MND patients (8 with bulbar onset and 8 with limb onset) and 8 healthy, age-matched controls. Metabolite concentrations were determined using the water signal as an internal standard. In contrast to the findings of reduced metabolite concentrations described above,[22,97,104] no differences were found in the concentrations of NAA, Cr, or Cho in the motor region of the total MND group compared to controls. In addition, no differences were found in NAA concentrations in the bulbar-onset group compared to the limb-onset group. Rather, the concentration of Cr was significantly higher in the subcortical white matter of the bulbar-onset group ($p = 0.04$), possibly as a result of gliosis in the motor region. These results suggested that Cr concentration may not remain stable in MND and its elevation would result in an apparent reduction of the NAA/Cr ratio.

The only ^{1}H-MRS study to date of cognitive decline in ALS was done at 4 T using single voxel short TE (TE 20 ms, STEAM) to evaluate prospectively over 6 months the anterior cingulate and right primary motor cortex of patients ($n = 13$) and spousal control subjects ($n = 5$).[99] At the initial scan, bulbar-onset ($n = 5$) but not limb-onset ($n = 8$) ALS patients showed significantly decreased NAA/Cr in cingulate ($p < 0.05$) and motor ($p < 0.001$) cortices. On repeat study 6 months later, six limb-onset patients showed significant reductions of NAA/Cr ($p < 0.05$) in the same regions. Decreased NAA/Cr indicating neuronal dysfunction or loss was present in the anterior cingulate gyrus early in the course of cognitive impairment and correlated with its appearance.

Multi-voxel ^{1}H-MRS

A multi-slice, multi-voxel ^{1}H-MRSI analysis of frontoparietal cortex and subcortical CST pathways revealed regional decreases of NAA/(Cho+Cr) in 10 patients with definite or probable ALS compared with 9 normal subjects.[96] Reductions in this ratio were significant ($p = 0.02$) in motor cortex (19%) and the subcortical CST (corona radiata and posterior limb of the internal capsule; 16%) but not in frontal cortex, parietal cortex, medial gray matter, or anterior internal capsule. A significant positive correlation was noted between the cortical NAA/(Cho+Cr) ratios and maximum finger-tap rate ($r = 0.80$, $p = 0.01$), a sensitive test of UMN function. These results further suggest that decreased cortical NAA signal is an objective and quantifiable surrogate marker of cortico-motoneuron loss in ALS. The same data were reanalyzed with improved techniques, which included automated curve fitting (to obtain metabolite concentrations) and tissue-volume correction (to co-register MRI and MRSI for better localization).[88] The results were essentially the same as in the original report with two important exceptions. A 23% reduction of absolute NAA signal was confirmed in the motor cortex of patients with ALS ($p = 0.004$) but not in the posterior limb of the internal capsule. Rather, the absolute Cho signal was increased in the latter region by 20% ($p = 0.02$) and not elsewhere. This suggests that the decreased NAA/(Cho+Cr) ratio in the original study was not the result of an absolute reduction in NAA. The increased Cho signal in the posterior limb of the internal capsule also correlated positively with increased UMN impairment ($r = 0.68$, $p < 0.05$). Release of choline phosphoglycerides following cell membrane damage from demyelination or increased lipid turnover from neuroglial proliferation could increase Cho signal.

^{1}H-MRS has been used to examine the potential effects of pharmacotherapies on the brains of patients with ALS. The first drug whose effect has been examined is riluzole (Rilutek®), a glutamate antagonist that prolongs survival and time to tracheostomy in patients with ALS.[107] After 3 weeks of standard riluzole therapy in 11 patients, NAA/Cr in the precentral gyrus increased from 2.14 ± 0.26 to 2.27 ± 0.24 ($p = 0.04$), whereas in 12 untreated patients it decreased from 2.17 ± 0.20 to 2.08 ± 0.20 ($p = 0.099$).[101] The change in NAA/Cr between the treated and untreated groups was 0.22 ± 0.095 ($p = 0.008$). There was no correlation between the degree of NAA/Cr increase and age, sex, duration of treatment or disease, the presence of

probable or definite UMN signs, bulbar features, or pretreatment NAA/Cr. The explanation of the increased NAA/Cr in the riluzole-treated patients, which did not persist, is unclear but may reflect at least temporary preservation of neuronal functioning and health in ALS. However, another study did not detect any effect of riluzole treatment for 2 weeks on NAA concentration in the precentral gyrus, although it is unclear how many patients were examined for this effect.[104]

A multimodal study with ^{1}H-MRSI, whole-brain DTI (along 25 noncollinear directions), and conventional T2- and FLAIR-weighted imaging was performed on 8 patients with definite ALS (6 limb-onset, 2 bulbar-onset) and healthy age-matched controls (12 for DTI, 5 for ^{1}H-MRSI) to study the CST.[108] FA and MD, and the ratio of *N*-acetyl-aspartate (NAA) to creatine (Cr) were measured along the CST, including the subcortical white matter (SWM), centrum semiovale (CS), periventricular white matter (PV), posterior limb of the internal capsule (PIC) and cerebral peduncle (CP). Conventional T2- and FLAIR-weighted MRI revealed hyperintensities along the CST in four of eight patients in the PIC ($n = 2$) and CP ($n = 2$). Compared with controls, patients had significantly lower FA ($p = 0.001$) but only slightly higher MD ($p = 0.19$) at all levels of the CST. In addition, NAA/Cr ratios were lower in the CST of ALS patients compared with normal controls ($p = 0.002$), although individual level differences reached significance only in the SWM and PV regions. The authors concluded that combined whole-brain DTI and MRSI yield the most robust results when examining the SWM and PV regions.[108]

SUMMARY

Neuroimaging of the patient with suspected ALS has traditionally been done to exclude other conditions that could mimic ALS. Such conditions typically cause compression or destruction of CNS and PNS structures, including cervical radiculomyelopathy, inflammation, and malignancy involving brain or spinal cord. However, in the past several years since the advent of MRI, abnormalities more specific to ALS have been identified in the CNS of patients with this disease. These primarily include hyperintensity of the corticospinal tract (seen on T2-, proton density- and FLAIR-weighted sequences) and hypointensity of the motor cortex (seen on T2-weighted sequences). Although not pathognomonic of ALS, these changes in the appropriate clinical setting strongly support this clinical diagnosis. Recent volumetric analyses have revealed that brain atrophy is a more common feature in ALS than previously appreciated, primarily in the pericentral region centered on the primary motor cortex and subcortical region.

Patients with ALS and FTD (ALS-FTD) tend to have more prominent brain atrophy than do patients with ALS alone. The atrophy is most often cortical, affecting premotor, prefrontal, and temporal lobe regions to varying degrees. Patients with prominent ALS-FTD rarely do not have obvious brain atrophy on MRI, possibly because the pathologic change is not as advanced as the functional deficit. Only recently, have some quantitative MRI studies documented cerebral atrophy in cases of ALS-FTD. A functional analysis using nuclear imaging techniques, such as PET, SPECT, or fMRI, may therefore reveal imaging abnormalities before brain atrophy is detected by routine MRI. The aforementioned CST hyperintensity and motor cortex hypointensity abnormalities can be found either separately or together in patients with ALS-FTD, indicating prominent pathology within motor pathways. ^{1}H-MRS, which is similar to standard MRI except that nonwater proton is imaged, has revealed decreased NAA, a marker of neuronal integrity, in the pericentral brain regions of patients with ALS. One study found that such abnormalities in ALS patients with cognitive decline occur maximally in the anterior cingulate gyrus, especially in those with bulbar onset.

Routine MRI, PET, SPECT, and ^{1}H-MRS studies have revealed abnormalities in the brains of patients with ALS but studies of patients with ALS-FTD are sparse. Clinico-radio-pathologic correlations using MR and nuclear imaging techniques would enhance our understanding of ALS-FTD in an effort to better characterize their co-occurrence, identify affected brain regions, and potentially elucidate pathogenic mechanisms. To achieve this, well

designed studies of patients with ALS-FTD using a variety of neuroimaging modalities should be performed.

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11

New approaches to imaging in ALS

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INTRODUCTION

The traditional view of amyotrophic lateral sclerosis (ALS) as a disease exclusively of the motor system has been revised in recent years. Cognitive impairment occurs in those suffering from the ALS-dementia syndrome but also in a significant proportion of patients with classical ALS.[1,2] The use of imaging techniques to explore the cerebral basis of cognitive change has had a major impact on neuropsychology and has advanced our understanding of ALS. Functional, structural and ligand techniques have been applied to ALS and revealed a consistent profile of extramotor cerebral dysfunction. The majority of studies have focused on patients with classical ALS and little research has been undertaken with patients with familial ALS or those suffering from the ALS-dementia syndrome. This chapter will describe some of this work and suggest future directions, with the application of new techniques, aimed at enhancing our understanding of ALS as a multisystem disorder.

COGNITIVE IMPAIRMENT IN ALS

The association of cognitive change and ALS has been reported for over a century, although the recognition of an ALS-dementia syndrome is a relatively recent concept. The case of a patient with progressive muscular atrophy and delirious confusion reported by Alzheimer[3] was possibly the first description of ALS-dementia. Later reports highlighted the rarity of this finding with discussion over whether a distinct ALS-dementia syndrome existed.[4,5] It was not until the 1980s that a more detailed description of this syndrome emerged with the publication of a series of cases.[6,7] It is now recognized that the ALS-dementia syndrome is not a chance association, and occurs in at least 5% of patients with classical ALS,[8] although some studies suggest that the prevalence is considerably greater when recent research diagnostic criteria for frontotemporal dementia (FTD) are used.[9] The syndrome is characterized by behavioral and cognitive change consistent with gross frontal lobe dysfunction with relative preservation of the functions of the posterior association cortices.[8,10–12] Pathological changes include spongiform neuronal degeneration in the prefrontal and temporal cortices[13–17] and regional involvement of the limbic system.[15,18–20] The molecular pathology hallmark of ALS-dementia is the presence of ubiquitin-immunoreactive inclusions in neurons of the frontal and temporal cortex, and in dentate granule cells of the hippocampus.[15,20–24]

Moreover, in the past 20 years there has been a wealth of neuropsychological evidence that cognitive change in ALS is not restricted to those suffering from overt dementia. A profile of

selective cognitive impairment has been repeatedly demonstrated in nondemented ALS patients predominantly characterized by executive dysfunction.[25] Deficits have been reported across a range of measures which assess cognitive flexibility, attention switching and monitoring, including standard and modified versions of the Wisconsin Card Sorting Test (WCST), letter and category fluency and the Trail Making Test.[26–31] Verbal fluency deficits have been the most striking and consistently reported impairment in ALS;[1,9,26,28,32–38] and deficits have been directly related to the presence of executive dysfunction.[34] This deficit has been shown to be independent of physical disability with the production of a verbal fluency index which controls for motor speed (Fig 11.1). Verbal fluency deficits have also been shown to be more pronounced although not exclusively found in ALS patients with pseudobulbar palsy[26] and, although present relatively soon after diagnosis, progression in nondemented ALS patients appears slow.[27] Memory impairments have been less consistently reproduced, with some studies reporting a deficit on specific tests of visual and verbal recall and recognition and others not.[1,29,35,37,39–41] With respect to basic language functions evidence of a word retrieval deficit (other than verbal fluency) has occasionally been demonstrated.[1,38,40–43] In extreme cases this may manifest as an ALS-aphasia syndrome, which is characterized by profound comprehension and expressive impairments, although many of these patients may also be suffering from the behavioral changes associated with ALS-dementia.[44]

$$\text{VFI} = \frac{\text{Time allowed for test} - \text{Time to copy words}}{\text{Number of words produced}}$$

Fig. 11.1 Verbal fluency index (VFI). Calculation of the verbal fluency index: estimate of the average time taken to think of each word. The index has been most frequently used with the Written Verbal Fluency Test in which the participant writes as many words as they can beginning with the letter S in 5 minutes followed by as many words as they can beginning with the letter C in four minutes, but which only have four letters (time allowed for test in total = 9 minutes). The participant is subsequently asked to copy the words they have previously written from which a measure of motor speed is obtained (time to copy words). A deficit in ALS patients has been repeatedly found using this measure, which is independent of physical impairment. In addition this test has been shown to be a sensitive indicator of extramotor dysfunction on both functional[33] and structural[62] imaging techniques.

ABNORMALITIES IN CEREBRAL FUNCTIONAL SYSTEMS

The amalgamation of functional imaging and neuropsychological methods has been particularly useful in investigating cognitive change in ALS. These approaches have revealed functional abnormalities predominantly in the prefrontal cortex associated with a corresponding cognitive profile of executive dysfunction. Early investigations measured changes in cerebral glucose metabolism or blood flow in patients in a resting state as indirect measures of neuronal functional integrity. Later investigations directly related cognitive performance to functional cerebral changes with the use of activation paradigms.

Several studies have used the positron emission tomography tracer 2-[^{18}F]-2-deoxy-D-glucose (FDG-PET) to measure regional changes in glucose metabolic rate (rCMRG). Reduced glucose utilization was demonstrated in most cortical areas and in the brainstem and basal ganglia in ALS patients with upper motor neuron signs.[45] Hatazawa et al.[46] found greatest reductions in the sensorimotor cortex and putamen, while Ludolph et al.[37] demonstrated clear extramotor involvement with reductions in the frontal and entire cortex in 18 ALS patients, some of whom were shown to have deficits on tests of executive functions (verbal and nonverbal fluency). Moreover the latter authors found a positive correlation between reduced rCMRG in the whole cortex, thalamus and caudate nucleus and verbal fluency scores.[37] At the same time other investigations employed single-photon emission computed tomography (SPECT) to demonstrate extramotor abnormalities in regional cerebral blood flow (rCBF) in ALS.[14,37,47] Again, some studies attempted to directly relate these imaging data to the profile of cognitive change. Talbot et al.[30] revealed pronounced rCBF reductions in frontal and anterior temporal cortices in nondemented ALS

patients who demonstrated evidence of subtle executive dysfunction with deficits on picture sequencing and a tendency towards poorer performance on verbal fluency and the WCST. In a study of 26 ALS patients Abe et al.[32] revealed reduced isotope uptake in frontal regions, this being most prominent in ALS patients with more severe deficits on tests of attention and executive function.

Cognitive dysfunction in ALS has been more directly investigated with the application of activation paradigms within functional imaging. This was initially achieved using the water-based PET tracer $H_2{}^{15}O$ to provide a measurement of rCBF. PET has been shown to be superior to SPECT blood flow measurement in image resolution and the technique can more readily provide quantitative data on extramotor cerebral changes in ALS.[48] The first of these studies[49] employed a motor activation paradigm involving the random generation of movements in 12 ALS patients. The procedure compared rCBF during two conditions; paced joystick movements in a freely chosen (random) direction, and movements only in a forward direction (stereotyped). The comparison of blood flow during these two tasks was known to result in an activation contrast demonstrating increased blood flow in predominantly the frontal cortex in healthy controls.[50] A comparison between ALS patients and controls of activation contrasts revealed abnormalities (reduced activation) in the medial prefrontal cortex, anterior cingulate gyrus and parahippocampal gyrus in ALS patients. Of note, the study also demonstrated extramotor cerebral abnormalities during resting state with decreases in rCBF in premotor, motor, parietal and insular cortex in ALS patients. In a further study the ALS patients were divided into two groups (five impaired and five unimpaired patients) based on their performance on a written verbal fluency task. Both ALS groups displayed significant reductions in rCBF in the medial prefrontal cortex and parahippocampal gyrus. However, those who were impaired on verbal fluency showed additional marked abnormalities along a limbo-thalamic-cortical pathway including the anterior cingulate gyrus and anterior thalamic nuclear complex.[36] Hence following on from the investigation by Ludolph and colleagues[37] of abnormalities in glucose metabolism, these findings further demonstrated that extramotor cerebral dysfunction was more pronounced in patients with verbal fluency deficits.

The association between verbal fluency deficits and cerebral change was more directly explored in a further PET activation study in which verbal fluency was employed as the activating task.[33] Once again two groups of ALS patients were assessed, defined by the presence or absence of cognitive impairment on the written verbal fluency task. In this assessment the verbal fluency test had been adapted to accommodate for writing disabilities with the inclusion of a control condition for motor speed (see Fig. 11.1). The two groups were otherwise similar in terms of age, IQ and levels of anxiety and depression. The activating paradigm contrasted rCBF during two conditions, letter-based word generation and word repetition. The word generation condition involved a slowed paced procedure which ensured that even those with a cognitive impairment could produce the same number of words as controls during the scanning procedure. The contrast of rCBF during word generation and word repetition was known to produce increased rCBF (activation) in the prefrontal cortex and anterior cingulate gyrus in healthy controls.[51] The comparison of activation contrasts between the two patient groups revealed reduced activation in extensive prefrontal regions in ALS patients with impaired verbal fluency indices as compared with healthy controls and the cognitively unimpaired ALS patients. Activation abnormalities were revealed in the dorsolateral prefrontal cortex, lateral and medial premotor cortex, primary motor cortex, insular bilaterally. In addition there was clear evidence of subcortical involvement with reduced rCBF in the anterior thalamic nuclear complex. In contrast ALS patients who were cognitively unimpaired showed a relatively normal pattern of rCBF activation. These results were found despite matched performance on the fluency task during scanning, suggesting that deficits in verbal fluency appeared to be a strong indicator of cerebral (predominantly prefrontal) dysfunction. However, it should be noted that subsequent analysis revealed that those ALS

patients with verbal fluency deficits were also impaired on other tests of executive and memory function including the WCST, the generation of random movements, paired associate learning and a test of object recall.

Such investigations have led to the application of functional magnetic resonance imaging (fMRI) to investigate linguistic and executive processes further. fMRI has advantages over PET in being noninvasive and more widely available. Here blood oxygenation level-dependent (BOLD) changes are measured, which reflect regional increases in blood flow assumed to reflect neuronal activation during motor or cognitive tasks. A recent study further investigated cognitive and cerebral change in 28 ALS patients and used 2 word retrieval paradigms, verbal fluency and confrontation naming to determine whether abnormalities were specific to verbal fluency activation tasks.[42] Although fluency and naming both involve word retrieval processes the former strongly relies on intact executive resources as words are intrinsically generated with few external cues to aid retrieval. In contrast, during naming the participant is required to find a word which corresponds to a picture of an object; hence the word to be retrieved is more fully specified by the external cue and there is little demand on executive processes. The imaging technique consisted of a compressed sequence blocked design which permitted the use of overt responding during scanning, which is of vital importance in measuring performance output in patient groups.[52] A comparison between ALS patients and healthy age-matched controls of BOLD changes during verbal fluency revealed significantly impaired activation in middle and inferior frontal gyri (dorsolateral prefrontal cortex) associated with the executive component of the task and anterior cingulate thought to be involved with the attentional aspects of the task in addition to regions of the parietal and temporal lobes associated with phonological storage and processing (see Fig. 11.2). Analysis of the naming paradigm also revealed impaired BOLD

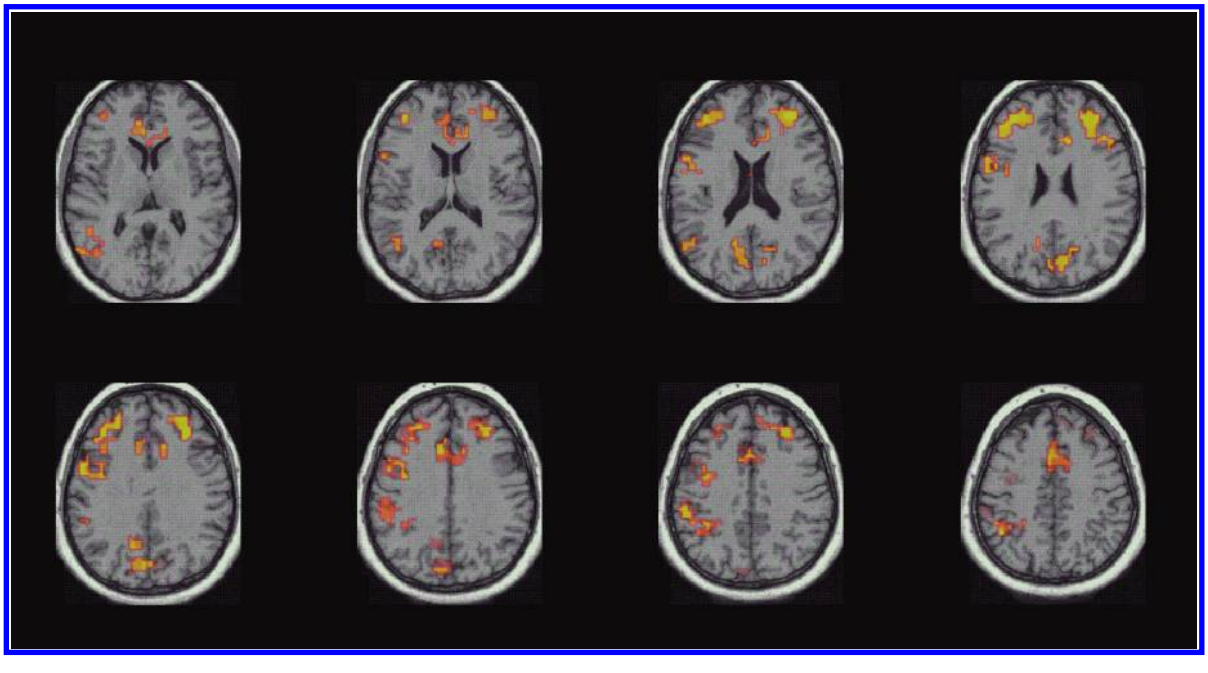

Fig. 11.2 Reduced fMRI BOLD changes in ALS patients (n = 28) relative to controls (n = 18) in the verbal (letter) fluency activation paradigm.[42] Axial slices parallel to the AC–PC plane are displayed for Talaraich z coordinates +6 mm, +11 mm, +16 mm, +21 mm (above) and +26 mm, +31 mm, +36 mm, +41 mm (below). Clusters of significant difference in BOLD changes are found in the right anterior cingulate gyrus, left inferior parietal lobe, left middle frontal gyrus, right middle frontal gyrus, left inferior frontal gyrus, left precuneus, and left middle temporal gyrus. Reproduced from Abrahams et al[42] with permission of Oxford University Press.

activation in less extensive prefrontal areas including the inferior frontal gyrus (including Broca's area) associated with language production and word retrieval and in the occipitotemporal pathway associated with the ventral pathway involved in object recognition. These changes were seen despite matched performance during scanning. Of note, neuropsychological assessment of these patients revealed not only verbal fluency deficits, but also an impairment in confrontation naming. Hence this study revealed that abnormalities were not specific to verbal fluency paradigms but involved the network of regions associated with both language and executive functions. The abnormalities found were more extensive than previously reported in the verbal fluency study using PET, but the study here consisted of a larger and possibly a more heterogeneous patient group. In addition, the fMRI group here were not selected on the basis of cognitive ability and hence more likely represented the scope of the disease. Hence the findings highlighted the heterogeneity of cognitive and cerebral change in ALS, with predominant executive dysfunction, but language networks can also be involved.

STRUCTURAL ABNORMALITIES IN CEREBRAL REGIONS AND PATHWAYS

The demonstration of extramotor abnormalities remained elusive in early structural imaging studies. However, the development of more specialized methods for acquiring and analyzing structural MRI data has enabled the detection of subtle cortical and subcortical changes in ALS.

Early structural imaging studies typically revealed atrophy restricted to the motor cortex and corticospinal tracts in nondemented ALS patients using computerized tomography (CT)[35,53] and MRI.[54–57] A study conducted by David and Gillham[58] succeeded in detecting cerebral atrophy in 8 of 14 ALS patients using CT, however these data were not quantified and hence no correlations could be attempted with neuropsychological measures.

The application of more sensitive MRI techniques has provided evidence of extramotor changes in cortical and subcortical structures. An investigation conducted by Kiernan and Hudson[59] employed volumetric MRI measurements and revealed shrinkage in the volume of the underlying white matter in the anterior frontal cortex in 11 nondemented ALS patients, but no significant frontal cortical atrophy. In a longitudinal study of ALS, progressive atrophy of the frontal and temporal regions was demonstrated using serial CT and MRI.[60] Atrophy was initially detected in the frontal and anterior temporal lobes, which progressed to the pre- and then post-central gyrus, anterior cingulate gyrus and corpus callosum. Three of the patients were also demented, although frontotemporal degeneration was not restricted to these patients. However, in neither of these imaging studies were the data related to neuropsychological findings.

In contrast, Frank et al.[28] obtained volumetric MRI data on 74 patients with ALS who were divided into two groups based on the presence or absence of neuropsychological impairments (with impairment reflecting deficits in verbal fluency, visual attention and visual memory). The impaired group showed more pronounced general cerebral changes of ventricular enlargement and parenchymal atrophy. Abe et al.[32] more specifically demonstrated frontal lobe atrophy as detected by visual assessment of MRI scans in patients with the most severe deficits in attention and executive functions who also demonstrated corresponding rCBF abnormalities using SPECT. Evidence of structural abnormalities has also come from reports of hyperintense signals in the white matter in frontal and temporal regions in ALS patients,[60,61] although such changes were not found in a more recent investigation of ALS patients with and without verbal fluency deficits.[62]

The use of new automated methods of performing voxel-based volumetric MRI analysis with the potential to delineate (or 'segment') gray and white matter has provided further evidence of the specific structural abnormalities in ALS. This method refers to the detection of regional differences between 3-D MRI images on a voxel-by-voxel basis after the process of spatial normalization of groups of images. Automated software is used to segment images to provide an estimation of gray and

white matter volumes and to perform direct comparisons between patients and controls at the voxel level. In the first study which used this method in ALS, Ellis et al.[63] compared 16 patients with healthy controls and revealed localized changes in the gray matter in the superior, medial and mid frontal gyrus. White matter abnormalities were restricted to the corticospinal tract of eight patients with a bulbar-onset form of the disease in contrast with eight limb-onset patients. It was suggested that these findings could be accounted for by a 'dying back' process in ALS. However, neuropsychological profiles were not reported. In a recent study Abrahams et al.[62] used this technique to investigate the relationship between verbal fluency deficits and underlying structural change. Two groups of ALS patients were once again investigated, defined by the presence or absence of a deficit on verbal fluency indices. In contrast to the above findings no differences were found in gray matter volumes. However, the group of 11 impaired patients revealed reduced white matter changes in extensive motor and extramotor regions including those corresponding to the frontotemporal association fibers (see Fig. 11.3). White matter abnormalities could be seen in regions through which run the long association bundles, which connect frontal and temporal lobes to other cortical regions. These include the occipitofrontal fasciculus, extending from the frontal lobes to the occipitotemporal regions, the superior longitudinal fasciculus, extending from the frontal poles to the occipital lobes and posterior parts of the temporal lobes, and the cingulum, which forms part of the limbic system and also has connections with the frontal cortex. In addition, reductions were found in regions through which run the anterior commissure, which connects the temporal poles, and the inferior longitudinal fasciculus, which extends from the temporal pole to the occipital lobe. Patients who were unimpaired on the verbal fluency indices

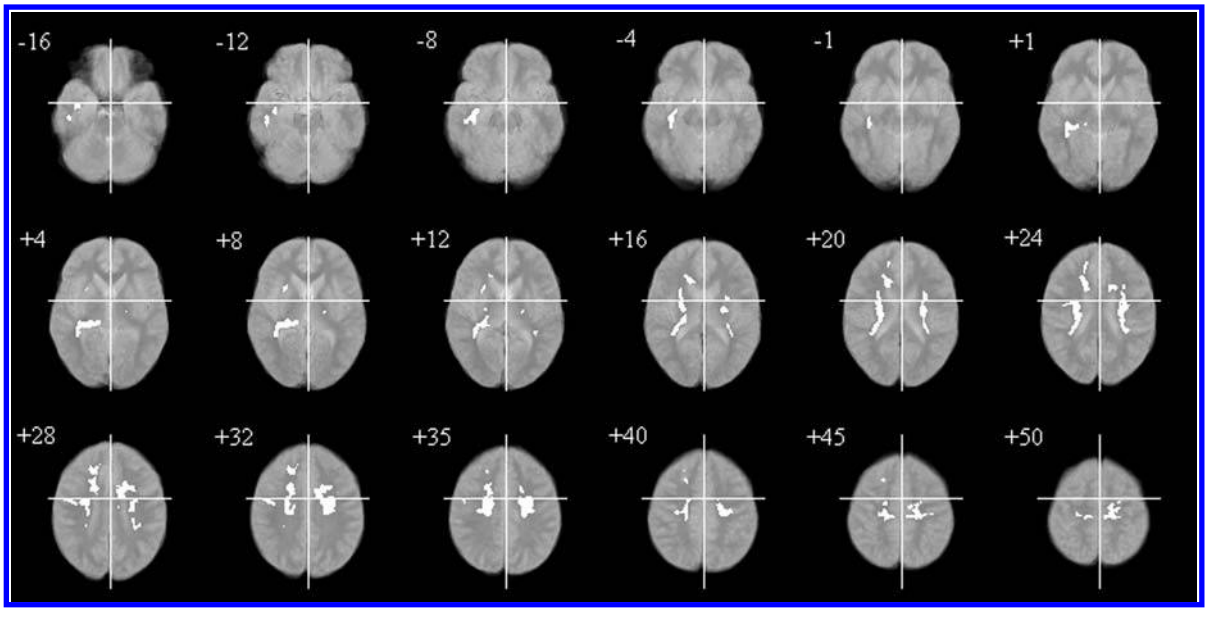

Fig. 11.3 Reduced white matter volumes in voxel-based analysis of structural MRI data.[62] ANCOVA map showing areas of significant ($p < 0.002$) reduction in white matter density (in white) in the ALS patients who were impaired on verbal fluency ($n = 11$) relative to the control ($n = 12$) group. Talairach z coordinates are shown below each slice. Right and left sides are reversed. Centroids of the clusters in the right internal capsule and left corona radiate, although regions include frontotemporal association fibers. From Abrahams S, Goldstein LH, Suckling J, et al. Fronto-temporal white matter changes in patients with amyotrophic lateral sclerosis. J Neurol 2005; 252:321–31, with kind permission of Springer Science and Business Media.

displayed a less extensive pattern of white matter volume reductions in frontal association fibers in comparison with controls. These included regions involving fibers connecting the frontal lobes to other cortical regions (cingulum, occipitofrontal fasciculus and the corpus callosum, particularly the forceps minor which extend into the frontal lobes). In addition, involvement of more posterior association fibers was also revealed with white matter reductions in areas corresponding to the splenium and forceps major of the corpus callosum. These findings suggest that white matter abnormalities may underlie both cognitive and functional changes revealed in previous investigations. Furthermore, the demonstration of such structural changes in cognitively unimpaired patients suggests that such abnormalities may precede cognitive change.

THE CELLULAR BASIS OF EXTRAMOTOR ABNORMALITY

Neuronal change can be more directly investigated through the application of imaging techniques based on the detection of ligand binding to neuronal receptors. The PET ligand flumazenil binds to the γ-amino butyric acid $(GABA)_A$ receptor which is found on neurons throughout the cortex. [^{11}C]-Flumazenil PET may therefore provide a marker of cortical neuronal loss/dysfunction or altered GABAergic inhibitory function, or indeed both. Lloyd et al.[64] initially demonstrated extensive motor and extramotor cortical reductions in flumazenil binding in a small group of ALS patients compared with healthy controls. In a larger study of 24 sporadic ALS patients decreases were localized to the motor cortex, posterior motor association and pre-motor regions[65] (see Fig. 11.4). Of note, the degree of clinical upper motor neuron involvement correlated with widespread cortical reductions over the left hemisphere. In an attempt to look at the heterogeneity of extramotor involvement in ALS, Turner et al. also investigated the binding in patients homozygous for the 'D90A' superoxide dismutase-1 (*SOD1*) gene mutation on chromosome 21; 5–10% of ALS cases have mutations of this gene, and most are dominantly inherited. The D90A *SOD1* gene mutation is usually inherited as a recessive trait. Homozygous patients (homD90A) show a characteristic and predictable phenotype beginning with lower limb spasticity and paresis prior to upper limb and bulbar involvement, with slow progression and long survival – averaging 14 years. In this group flumazenil binding decreases were found in the left frontotemporal junction and anterior cingulate gyrus, suggesting a different pattern of cerebral involvement in these patients in comparison with sporadic ALS.

The PET ligand WAY100635 is selective for the serotonin 5-HT_{1A} receptor. These receptors are found on pyramidal neurons throughout the cortex and reductions in receptor binding may therefore reflect loss or damage to neurons bearing those receptors. Turner et al.[66] investigated 21 nondepressed ALS patients compared with controls using [^{11}C]-WAY 100635. The ALS patients displayed a 21% reduction in global cortical and raphe binding (see Fig. 11.5). A region of interest analysis of all cortical regions revealed reductions in binding of between 16 and 29% in ALS patients compared with controls. The regions of the greatest differences were in the frontotemporal regions, cingulate gyrus and lateral precentral gyri. These reductions were not thought to be related simply to depression, the diagnosis of which was an exclusion criterion, with symptomatic screening carried out using the Hospital Anxiety and Depression Scale.[67] Similarly the changes were not thought to relate to riluzole or other drug therapy.

The PET ligand PK11195 binds to the peripheral benzodiazepine binding site (PBBS), expressed by cells of the mononuclear phagocyte lineage. Within the central nervous system PBBS is highly expressed by activated (not resting) microglia. PK11195 can therefore be used to measure microglial activation in brain disease and has proved a sensitive *in vivo* marker of other progressive neurological conditions, including Alzheimer's disease.[68] There is evidence that inflammatory mechanisms, in which microglial cells may play a vital role, are important mediators of cell death or survival in ALS[69] and there are a number of hypotheses concerning selective motorneuronal cell death.[70] In addition, drugs which specifically

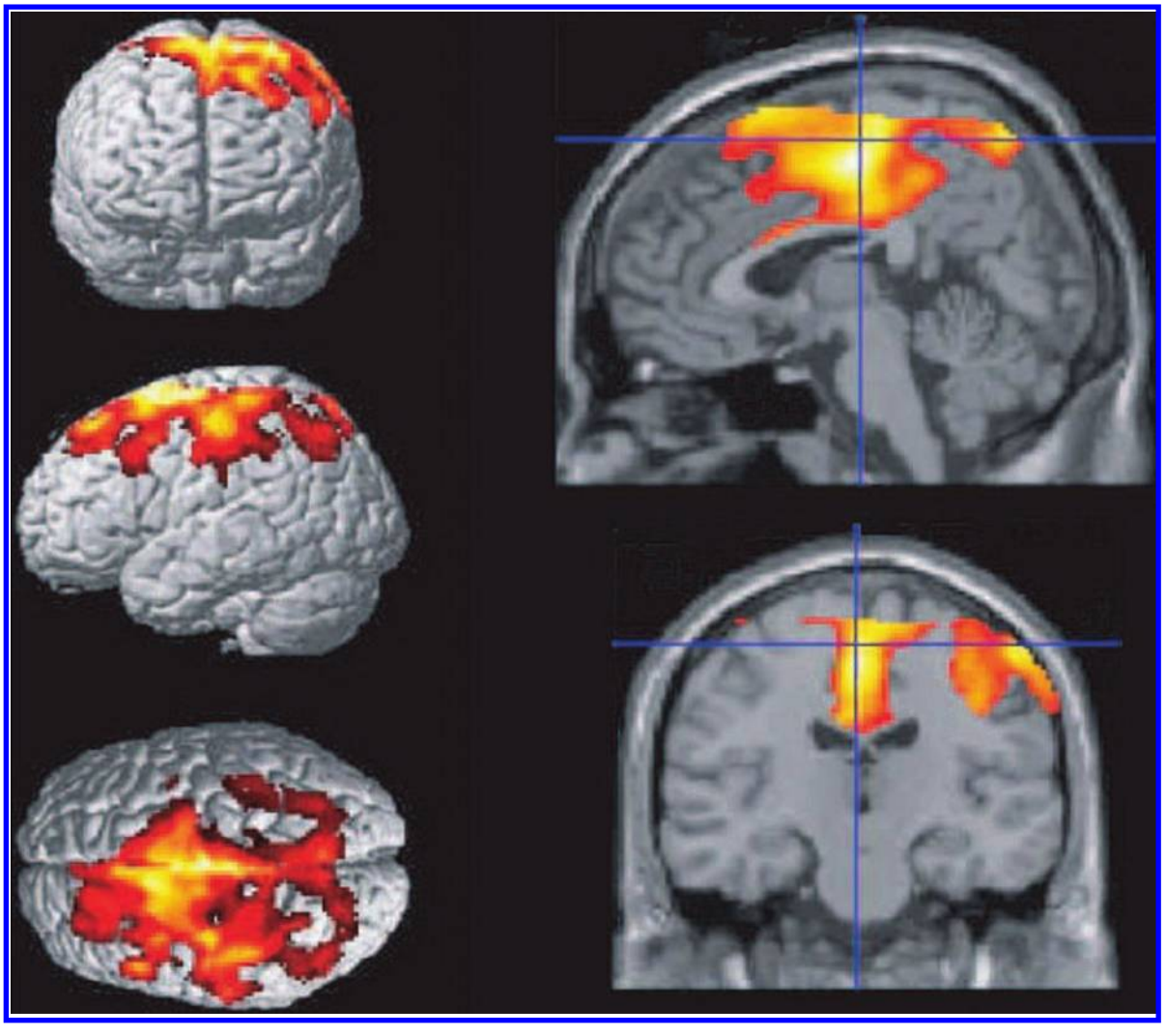

Fig. 11.4 Decreases in the cortical binding of [11C]-flumazenil in an ALS group, compared with controls.[65] Significant (corrected) clusters of decreased binding are seen bilaterally over the premotor regions, motor cortex (including the medial hemispheric surface) and in posterior motor association areas. Reproduced from Turner et al[65] with permission of Oxford University Press.

affect the inflammatory pathways have been shown to affect survival in transgenic mouse models of ALS.[71] Turner et al.[72] compared 10 ALS patients with controls using the [^{11}C]-PK11195 ligand and demonstrated widespread microglial activation in both motor (pons and motor cortex) and extramotor regions including the dorsolateral prefrontal cortex and thalamus (Fig. 11.6.). Severity of clinical upper motor neuron involvement correlated with degree of cerebral change, particularly in the thalamus and motor cortex.

Evidence of neuropathological change underlying such imaging abnormalities has been scarce. However, a recent study has demonstrated loss of pyramidal neurons and a subpopulation of GABAergic interneurons in extramotor regions in ALS, which would be consistent with these ligand studies. Maekawa et al.[73] investigated 13 ALS patients as compared with 8 controls and demonstrated significant reductions in the density of SMI-32 (nonphosphorylated neurofilament heavy chain) immunoreactive pyramidal neurons in cortical layer V of the primary

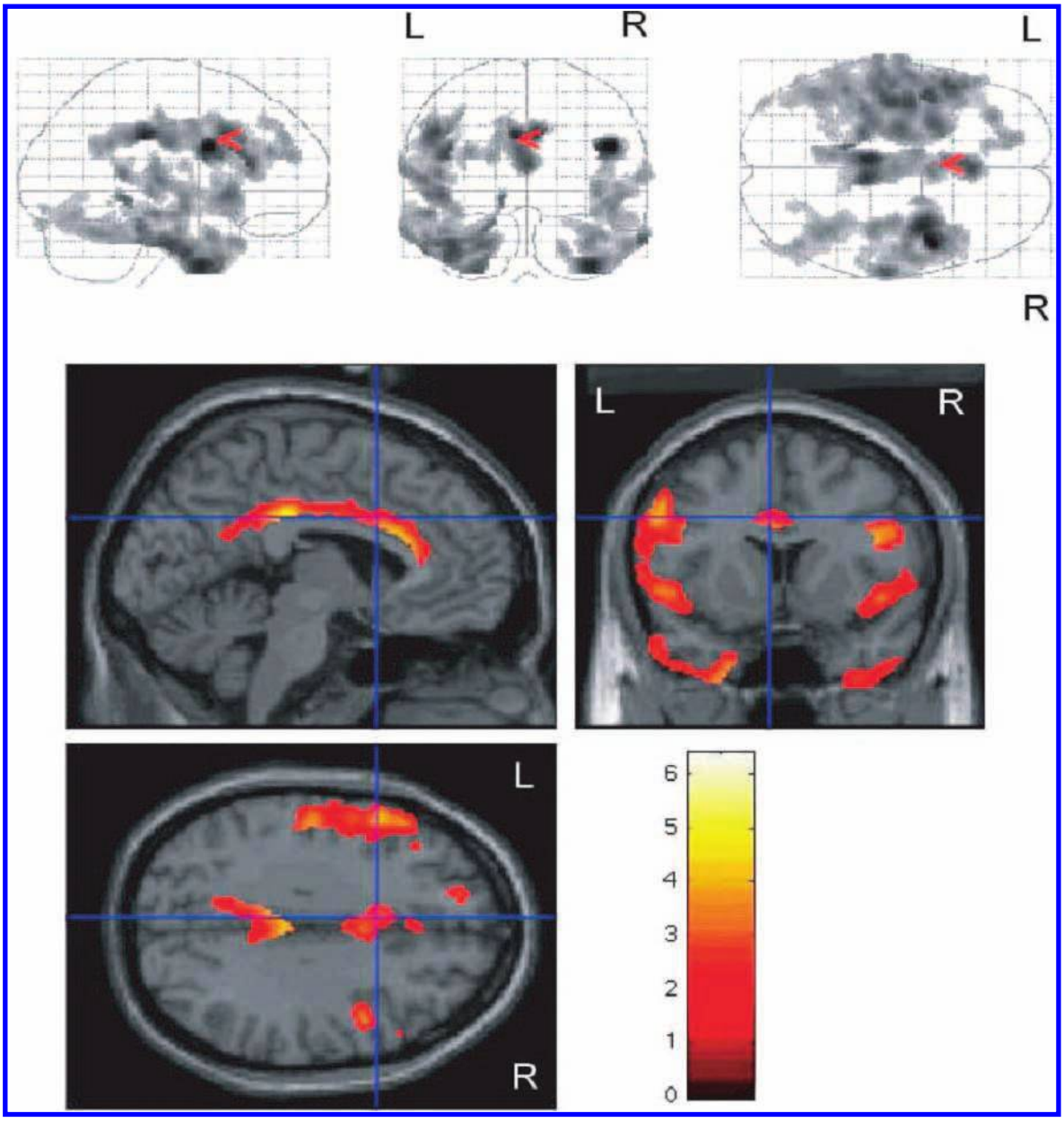

Fig. 11.5 Decreased [11C]-WAY100635 binding in ALS group compared with controls.[66] Statistical parametric map displayed on the generic 'glass brain' format and T1 MRI below (left and right hemispheres are labeled accordingly). Using this method the cluster-corrected regions of greatest reduction ($p < 0.05$) in the binding potential of [11C]-WAY100635 in ALS patients compared with controls lie mainly within the temporal and posterior frontal lobes, including the cingulate and lateral precentral gyri. The Z-score is shown as a color scale. Reproduced from Turner et al[66] with permission of Oxford University Press.

motor cortex, dorsolateral prefrontal cortex and anterior cingulate gyrus. In addition, there was a significant reduction in the density of GABAergic interneurons immunoreactive for calbindin-D_{28K} in cortical layers V and VI in the same regions. These findings directly demonstrate neuronal degeneration in regions outside the motor system in ALS. The loss of cortical projection neurons in

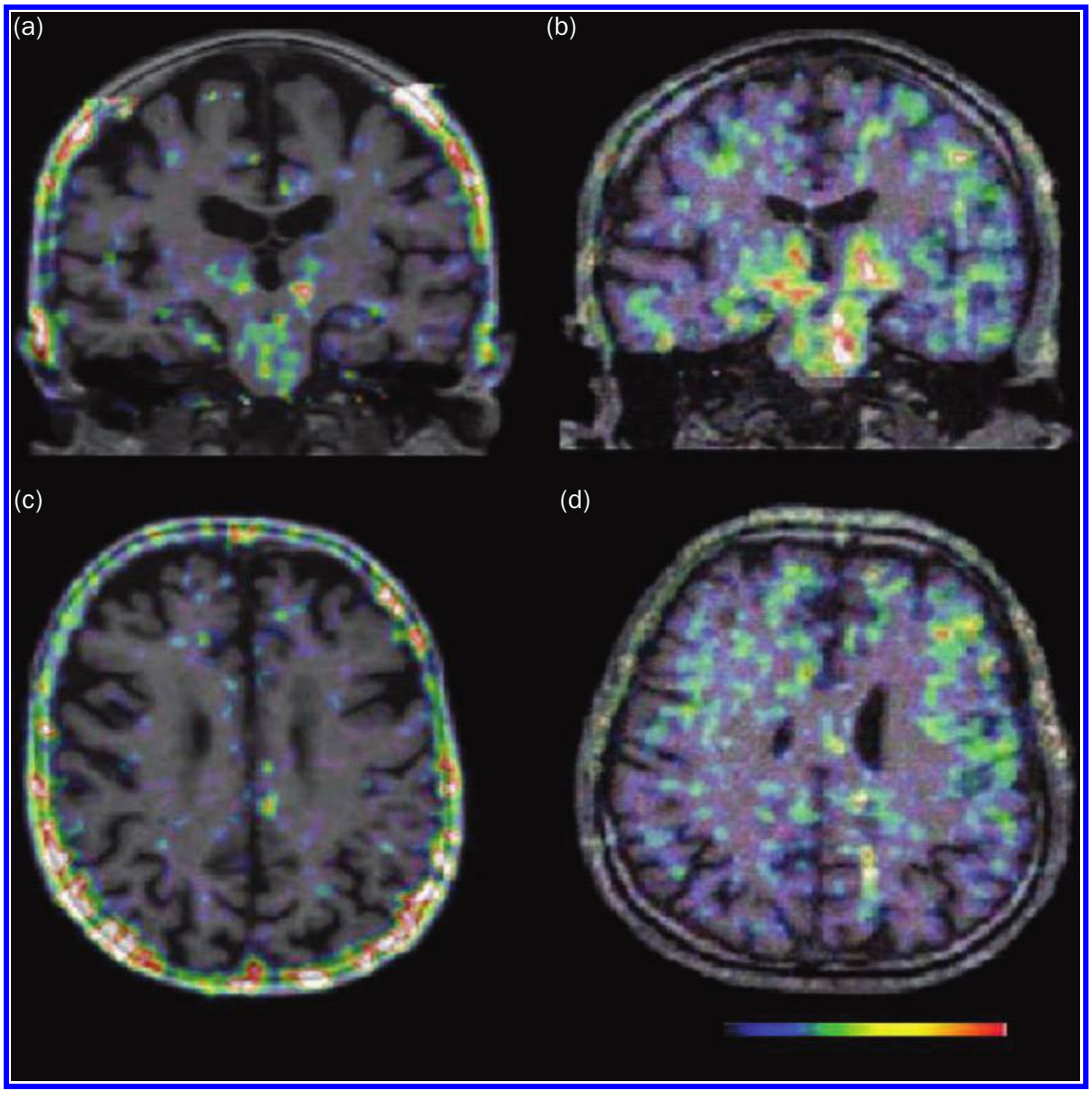

Fig. 11.6 [11C](R)-PK11195 PET binding potential maps co-registered with T1-weighted MR images in control (a, c) and ALS patients (b, d).[72] Increased signal in the region of the thalamus and pons (b); and frontal lobe (d) in ALS patients (coronal and transverse sections). The color scale is calibrated for [11C](R)-PK11195 binding. Reprinted from Turner MR, Cagnin A, Turkheimer FE, et al. Evidence of widespread cerebral microglial activation in amyotrophic lateral sclerosis: an [11C] (R)-PK11195 positron emission tomography study. Neurobiol Dis 2004, © with permission from Elsevier.

specifically the dorsolateral prefrontal cortex and anterior cingulate cortex suggests that this is the cellular basis of the clinical features of cognitive impairment in ALS.

FUTURE DIRECTIONS

The possibility of subcortical involvement of white matter tract fibers suggested by previous imaging studies[62] indicates that diffusion tensor imaging (DTI) may be a useful technique for further application in the study of extramotor cerebral change in ALS. DTI is a method for detecting the movement and directionality of water using MRI. In healthy neurons the movement of water is anisotropic in that it is restricted along the intact axonal fibers. When axons are damaged water molecules become isotropic. DTI

produces the measures of fractional anisotropy and mean diffusivity to reflect these changes in pathway integrity and previous studies have detected changes in these measures in the corticospinal tract in ALS patients.[74,75] It has yet to be demonstrated whether these methods can detect changes in regions such as the dorsolateral prefrontal cortex or anterior cingulate cortex in ALS. Also, the use of improved analysis techniques leading to increased signal-to-noise ratio and whole-brain analysis should allow for between-group comparisons without *a priori* regions of interest. This will allow a more comprehensive investigation of extramotor involvement. Other recent advances in DTI which have permitted the investigation of specific white matter tracts may also be a fruitful approach. DTI tractography has been used to delineate perisylvian language networks in healthy controls.[76] Using this methodology, tracts such as the arcuate fasciculus which connects Broca's and Wernicke's areas have been reconstructed and previously undescribed tracts connecting these regions to the parietal lobes have been reported. The application of such techniques to the investigation of those tracts involved in executive and language functions in ALS may shed more light on the cerebral changes underlying cognitive presentation.

Proton magnetic resonance spectroscopy (MRS) is a technique which has had limited success so far in detecting change in ALS. MRS involves the use of MRI to produce measurements of specific cerebral metabolites. Ratios of N-acetyl aspartate (NAA) to creatine, phosphocreatine or choline are thought to reflect neuronal dysfunction or loss, while other metabolites such as myoinositol, glutamate and glutamine have the potential to shed light on excitotoxic mechanisms which may be involved in ALS. This technique has been successful in detecting change within the corticospinal tract in ALS,[77] although once again it has not been applied to the investigation of extramotor regions. A promising finding has been shown in patients with primary progressive aphasia (PPA), a variant of FTD, which is associated with focal degeneration in language regions. Metabolites were measured in the superior longitudinal fasciculus which connects Broca's area with Wernicke's area and other regions of the temporal lobes. Patients with PPA displayed asymmetrical N-acetylaspartate to creatine ratio as compared with Alzheimer's disease patients with greater changes in the left hemisphere. Myoinositol to creatine ratio was also increased in the PPA group.[78]

Future studies in ALS may maximize their potential through the use of a combination of imaging techniques – a multimodal approach. Such methods will then enable the link to be made between structure and function and disease process to clinical manifestation. For example, the combined use of tractography and MRS would permit the investigation of the pathways and pathological mechanisms which mediate executive and language dysfunction in ALS. Links can then be made from cellular dysfunction to cognition. The amalgamation of neuropsychology and imaging methodologies has fundamentally shaped our understanding of ALS. The further union of neuropsychology, multimodal imaging and cellular and molecular pathology has the potential to substantially enhance our understanding of this disease and it is hoped shed light onto targeted therapeutic intervention.

ACKNOWLEDGMENTS

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12

Neuropathology of frontotemporal lobar degenerations

Nigel J Cairns

INTRODUCTION

After Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), frontotemporal lobar degenerations (FTLDs)[1–3] are the most common neurodegenerative disorders. They have a worldwide distribution and men and women are both affected. A family history of a similar dementing disorder has been reported in about half of all cases.[4,5] Most of the FTLDs are characterized by the pathological aggregation of misfolded proteins, either in neurons or glial cells, or both. About half of the cases have abnormal intracellular cytoplasmic accumulations of the microtubule-associated protein (MAP) tau. The term *tauopathies* has been applied to this apparently unrelated group of diseases, which includes Pick's disease (PiD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), neurofibrillary tangle dementia (NTD), argyrophilic grain diseases (AGD), and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17).

A second group of patients with FTLD lacks filamentous tau inclusions. The molecular classification of this group is evolving, but includes frontotemporal lobar degeneration (FTLD),[3,6] also called dementia lacking distinctive histopathology (DLDH)[4] or frontal lobe degeneration of non-Alzheimer type[7] (see Chapter 13), FTLD with motor neuron disease-type inclusions (FTLD-MND)[3] also called motor neuron disease-inclusion dementia[8] (see Chapter 13), neuronal intermediate filament inclusion disease (NIFID),[9] basophilic inclusion body disease (BIBD),[10] and frontotemporal dementia (FTD) with inclusion body myopathy and Paget's disease of bone.[11] The practicing neuropathologist should also be aware that sporadic and familial cases of FTD may be associated with AD and other neurodegenerative diseases including DLB.[12]

FTLDs WITH TAU INCLUSIONS

Several sporadic and familial neurodegenerative diseases are characterized by the formation of argyrophilic, filamentous deposits of abnormal brain proteins. Thus, a heterogeneous group of FTLDs is linked by the presence of pathological intracellular glial and neuronal inclusions of tau (Table 12.1). Despite the diverse phenotypic expression, brain dysfunction and

Table 12.1 Molecular classification of inclusion bodies in frontotemporal lobar degenerations

Disease	*Protein aggregate*	*Chromosomal linkage, gene defect/haplotype*	*Isoform*
FTLDs with tau inclusions			
PiD sporadic	Tau	Unknown	3R
PiD familial	Tau	*Presenilin 1 (PS1 M146L, G183V)*	3R
CBD sporadic	Tau	*Tau H1 haplotype*	4R
PSP sporadic	Tau	*Tau H1 haplotype*	4R; 4R > 3R
NTD sporadic	Tau	Unknown	3R and 4R
AGD sporadic	Tau	Unknown	4R
FTDP-17 familial	Tau	Chromosome 17 *Tau**	4R; 4R and 3R; 4R > 3R
FTLDs without tau inclusions			
FTLD sporadic	ND	Unknown	–
FTLD familial	ND	*CHMP2B*	–
FTLD familial	ND	Chromosome 17, *Tau* intron 10+19, +29*	3R
FTLD-U sporadic	Ubiquitin†	Unknown	–
FTLD-U familial	Ubiquitin†	Chromosome 9	–
FTLD-U familial	Ubiquitin†	Chromosome 17	–
BIBD sporadic	Ubiquitin†	Unknown	–
NIFID sporadic	Ubiquitin + neuronal intermediate filaments	Unknown	–
IBMPFD familial	Ubiquitin + valosin-containing protein	Chromosome 9 *Valosin-containing protein*	–

FTLD, frontotemporal lobar degeneration; FTLD-U, frontotemporal lobar degeneration with ubiquitin-positive, tau-negative inclusions, also called FTLD-motor neuron disease-type (FTLD-MND-type); AGD, argyrophilic grain disease; NIFID, neuronal intermediate filament inclusion disease; BIBD, basophilic inclusion body disease; IBMPFD, inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia; PiD, Pick's disease; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; NTD, neurofibrillary tangle dementia; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17; 3R, the predominant number of tau isoforms with three microtubule-binding domains; ND, not determined.
* Mutations in *tau* are described in Table 12.2. CHMP2B, charged multivesicular body protein 2B.
† Inclusions in these diseases contain ubiquitin, but other proteins have not yet been identified.

neurodegeneration are linked to the progressive accumulation of abnormal filamentous protein; and this, together with the absence of other disease-specific neuropathological abnormalities, provides evidence implicating tau in disease onset and progression. The discovery of multiple mutations in the *tau* gene in frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) has led to the unequivocal evidence that tau abnormalities alone are sufficient to cause neurodegenerative disease. These discoveries have opened up new avenues of research into the role of tau in mechanisms of brain dysfunction and neurodegeneration.

Tau proteins are low-molecular-weight microtubule-associated proteins (MAPs) that are abundant in the CNS where they are expressed predominantly in axons, and at low levels in astrocytes and oligodendrocytes. Human tau proteins are encoded by a gene on chromosome 17 of 16 exons with CNS isoforms generated by alternative mRNA splicing of 11 of these exons (Fig. 12.1). In adult human brain, alternative splicing of exons 2, 3, and 10 generates 6 tau isoforms ranging from 352 to 441 amino acids in length which differ by the presence of either 3 or 4 microtubule (MT) binding repeats (3R tau or 4R tau, respectively). Additionally, alternative splicing of exons 2 and 3 leads to the absence (0N) or presence of inserted sequences of 29 (1N) or 58 (2N) amino acids in the amino-terminal third of the molecule. In the adult human brain, the ratio of 3R:4R tau isoforms is approximately 1:1.

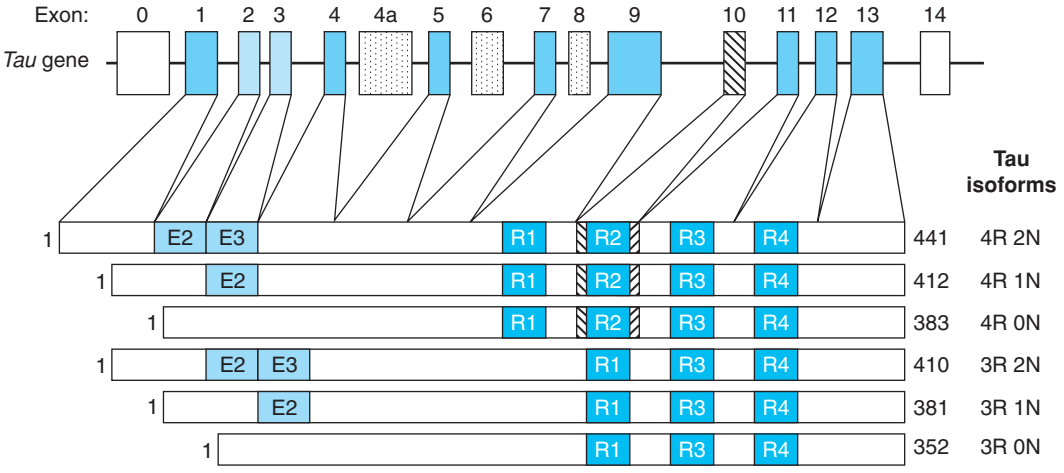

Fig. 12.1 Schematic representation of the human tau gene and six human CNS tau isoforms generated by alternative splicing. Alternative splicing of exons 2 (E2), 3 (E3) and 10 produces the six tau isoforms. The black bars depict the 18 amino acid microtubule binding domains and are designated R1 to R4. The relative sizes of the exons and introns are not drawn to scale.

Tau binds to and stabilizes MTs and promotes MT polymerization. The MT binding domains of tau are localized within the 4 MT binding motifs (Figs 12.1 and 12.2), which are highly conserved. The function of tau as an MT binding protein is regulated by phosphorylation. Several protein kinases and protein phosphatases have been implicated in regulating the phosphorylation state and thus the function of tau. However, in both sporadic and familial tauopathies tau is hyperphosphorylated, and it is this 'abnormal' tau that is the principal component of the filamentous aggregates in neurons and glia that are the pathological hallmarks of these disorders. The tauopathies may be broadly grouped according to the pattern of tau immunostaining and tau isoform ratios as demonstrated by Western blotting (Fig. 12.3).

PICK'S DISEASE

Arnold Pick first reported a form of presenile dementia with circumscribed lobar atrophy in 1892. However, it was Alois Alzheimer who first described the histological lesions that are characteristic of the disease – intraneuronal, argyrophilic, globular inclusions – in 1911. Classic cases of Pick's disease (PiD) may be readily distinguished from AD on clinical grounds but many PiD patients have symptoms which are indistinguishable from those found in AD. In contrast, it is easier to distinguish PiD from AD pathologically. Pick's disease is an uncommon cause of dementia and accounts for less than 5% of cases.[13] The age at onset varies between 45 and 65 years and rarely beyond 75 years. Thus, unlike most patients with AD, patients with PiD have, typically, an early-onset dementia. The duration of the disease is on average 5–10 years. Women appear to be slightly more affected than men and the disease has a worldwide distribution. It is largely a sporadic disease and as familial cases have come under greater scrutiny the original diagnosis in some has been revised to take account of advances in immunohistochemistry and molecular genetics. Most familial cases have now been reassigned to FTDP-17. However, in one family with tau-positive inclusions, a novel *presenilin 1* mutation was reported[14] demonstrating that PiD, like AD, is genetically heterogeneous. Two extended haplotypes cover the human *tau* gene and there is complete disequilibrium between polymorphisms that span the gene. This suggests that the establishment of the two haplotypes was an ancient event and either that recombination is suppressed in this region, or that recombinant genes are selected against. The more common

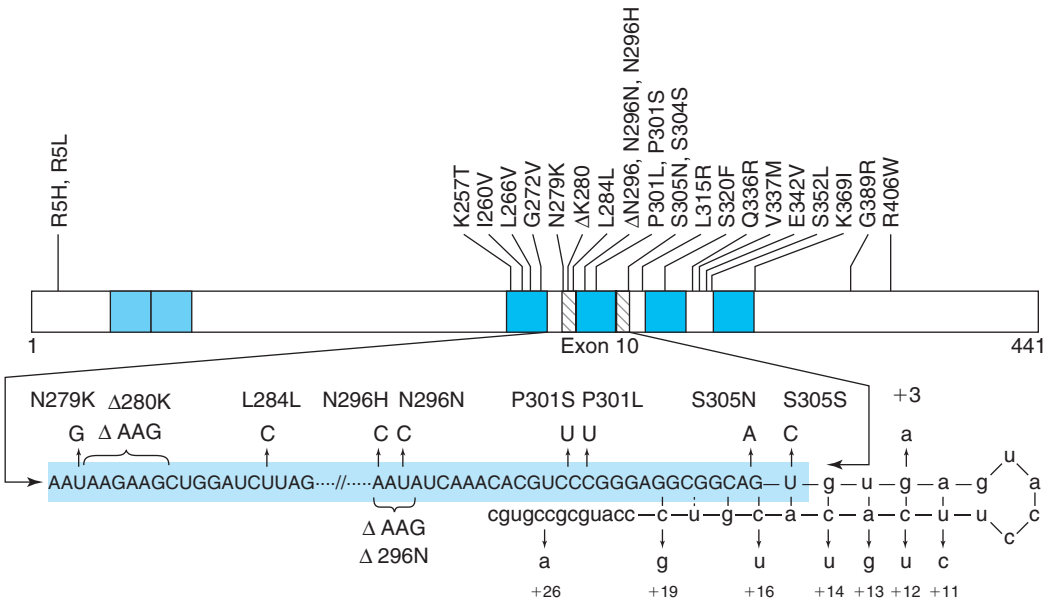

Fig. 12.2 Schematic representation of mutations in the tau gene in FTDP-17. The structure of the largest tau isoform is shown with known coding region mutations indicated above. The gray boxes near the amino terminus represent the alternatively spliced inserts encoded for by exons 2 and 3, while the black boxes represent each of the four microtubule (MT) binding domains (not drawn to scale). The second MT binding repeat is encoded by exon 10. Part of the mRNA sequence encoding exon 10 and the intron following exon 10 is enlarged to visualize the 5′ splice site as well as the mutations in both exon 10 and within the 5′ splice site. Nucleotides of intron 10 are shown in lower case.

haplotype (H1) is significantly over-represented in patients with progressive supranuclear palsy (PSP),[15] but there is no difference between the tau H2 haplotype or H2/H2 genotype frequency in PiD cases when compared with control subjects, and no tau mutations have been found in pathologically typical sporadic cases of PiD.[16]

The appearance of the PiD brain is one of the most dramatic in all neuropathology (Fig. 12.4). What is striking is the severity of atrophy and its localization to the frontal or temporal lobe, or both, and less commonly to the parietal lobe. The loss of tissue can be so severe as to give the appearance of a shrivelled walnut. In classic cases, the temporal pole may be particularly affected, with relative sparing of the posterior part of the superior temporal gyrus. The amygdala and hippocampus are often severely affected and the caudate nucleus may be so atrophied as to give the appearance of that seen in Huntington's disease. The lateral ventricles may be severely dilated. These changes can be contrasted with the relatively well-preserved remainder of the brain. Although these changes are typical of PiD, they may not be present in all cases. The patient may die at an early stage of the disease and the atrophy may not be particularly extensive. In those patients who have the longest clinical history the brain may be the most atrophied.

The diagnostic histological feature of PiD is the Pick body (Fig. 12.5b and c). Pick bodies are well-circumscribed, spherical, argyrophilic, tau-immunoreactive neuronal intracytoplasmic inclusions. In addition, there are swollen achromatic so-called 'ballooned' neurons or Pick cells, neuronal loss, and astrocytosis. Ballooned neurons have a slightly different immunohistochemical profile to that of Pick bodies. Like Pick bodies, swollen neurons are labeled by anti-ubiquitin, anti-tau, and anti-αB-crystallin antibodies (Fig. 12.5a).[17] Pick bodies are found most abundantly in the granule cells of the dentate gyrus and at lower densities in the pyramidal

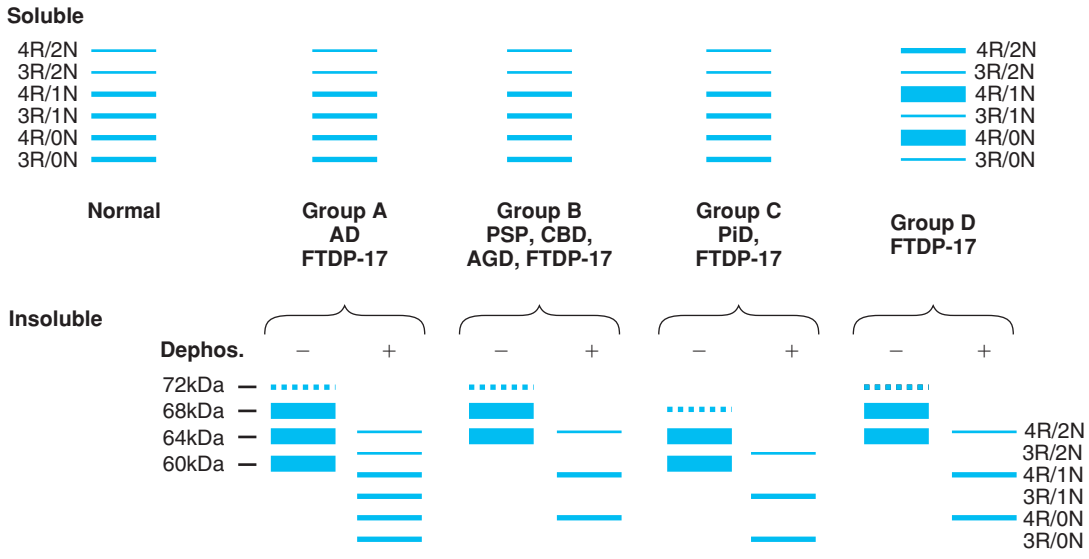

Fig. 12.3 Cartoon representing western blot banding patterns of soluble and insoluble tau from different tauopathies. The figure depicts the typical banding pattern of soluble tau (top panels) and insoluble and filamentous tau (bottom panels) from the brains of patients with FTDP-17, as well as sporadic tauopathies resolved by electrophoresis and demonstrated by immunoblotting with anti-tau antibodies. The FTDP-17 mutations show several different Western blot banding patterns of soluble and insoluble tau protein that are depicted as groups A to D. The soluble fraction from the brains of unaffected (normal) individuals, sporadic tauopathies, and FTDP-17 with mutations that do not affect tau splicing (groups A, B, and C) show expression of all six tau isoforms. Insoluble tau from the brain of patients with FTDP-17, group A (S320F, V337M, K369I, G389R, and R406W), resolve as three major proteins of 68, 64 and 60 kDa; and a minor band of 72 kDa similar to that observed in AD. When dephosphorylated, they resolve into six proteins that correspond to all six tau isoforms similar to the soluble fraction. In FTDP-17 group B (R5H, P301L, and G342V), two prominent 68 and 64 kDa protein bands are detected (the 72 kDa minor band is variably detected) that align with 4R tau following dephosphorylation similar to that observed in PSP and CBD, indicating the selective aggregation of 4R tau. In FTDP-17 group C (K257T) and PiD the 64 and 60 kDa insoluble tau protein isoforms predominate and align with 3R tau isoforms following dephosphorylation, indicating selective aggregation of 3R tau. In contrast, in FTDP-17 mutations that affect mRNA splicing (group D: N279K, L284L, N296N, N296H, S305S, S305N, and intron 10 mutations), there is expression of predominantly 4R tau throughout the entire brain which is reflected in the insoluble tau aggregates.

neurons of the frontal and temporal neocortex. The distribution of Pick bodies may be uni- or bilaminar and this difference may reflect the stage of progression of the disease. A prominent band may be seen in layer II and upper layer III and a band in layer IV. These neurons can be contrasted with those in AD where NFTs are found predominantly in the large pyramidal neurons of layers III and V, the major cortico-cortical projecting neurons. Spatial pattern analysis has shown that Pick bodies appear in regular clusters throughout affected cortical areas.[18] They may be found outside the hippocampus, temporal and frontal neocortex including the amygdala, striatum, thalamus, hypothalamus, brainstem nuclei, and the spinal cord.

Ultrastructurally, Pick bodies consist mainly of bundles of disorganized straight fibrils which are labeled by anti-tau antibodies. Although the Pick body is well demarcated by light microscopy, ultrastructurally it does not appear to have a limiting membrane. Immunohistochemically, Pick bodies are labeled most intensely by anti-ubiquitin and anti-tau antibodies. They have a similar staining pattern to NFTs, but the immunohistochemical and biochemical profile of tau in PiD is different from that in AD: in PiD, 3R tau isoforms are predominant.[19–21]

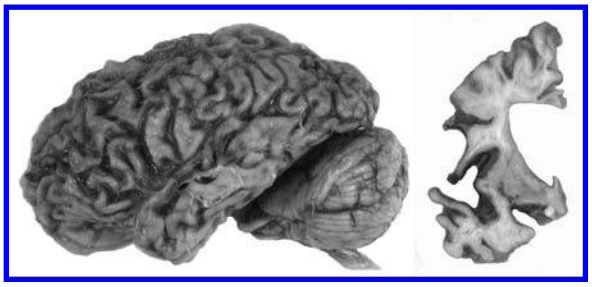

Fig. 12.4 Pick's disease. Left panel: There is striking atrophy of the frontal and temporal lobes and the parietal lobe is also affected. The gyri are markedly thinned and the sulci widened. Right panel: A coronal slice of the hemi-brain of the left panel. The lateral ventricle is severely dilated, the lateral fissure is enlarged, gyri are narrowed, and the cortical ribbon is thinned.

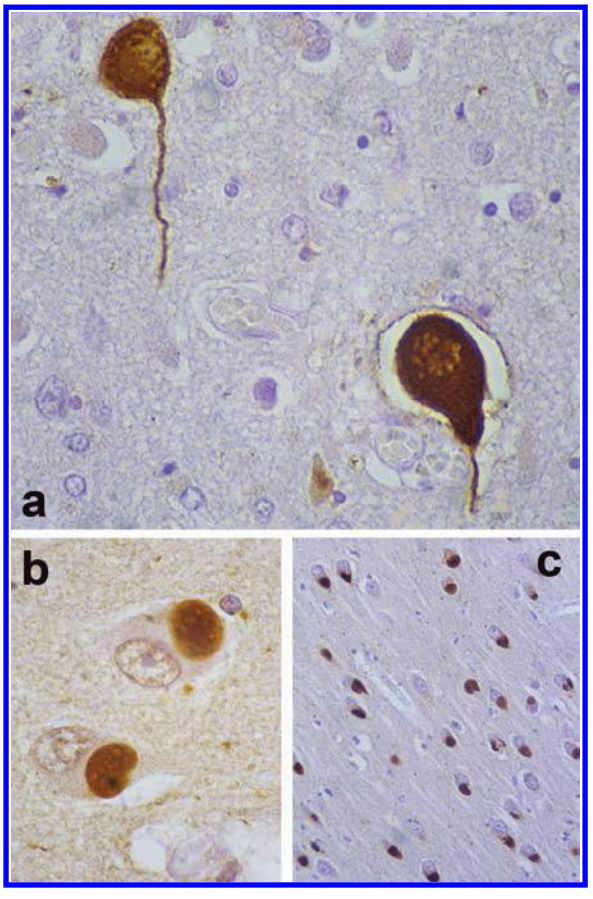

Fig. 12.5 Pick's disease. (a) Swollen achromatic neurons, so-called 'ballooned' or Pick cells, in the frontal lobe. αB-crystallin immunohistochemistry. (b) Pick bodies. Ubiquitin immunohistochemistry. (c) Numerous neuronal cytoplasmic Pick bodies in the subiculum. Tau immunohistochemistry.

CORTICOBASAL DEGENERATION

The clinico-pathological description of cortico-dentatonigral degeneration with neuronal achromasia was first made by Rebeiz, Kolodny, and Richardson in 1967 and 1968, but it was Gibb, Luthert, and Marsden who coined the term corticobasal degeneration (CBD) in 1989. Males and females are equally affected and the age at onset of sporadic cases is in the sixth to eighth decades. In the rare familial cases that have been reported, there is an earlier age at onset. Duration of illness ranges from 7 to 10 years. The neuronal and glial inclusions of CBD may be compared with those of PiD and PSP. The presence of swollen neurons, particularly when demonstrated by immunohistochemistry, is the most striking feature of this disease. As with familial cases of PiD, the discovery of mutations in the *tau* gene in familial cases of CBD has resulted in these cases being reassigned to FTDP-17. In sporadic cases, genetic analysis of the tau gene has resulted in two major forms, or haplotypes, called H1 and H2. The frequency of the H1 haplotype is increased in CBD and several cases are H1/H1 homozygous.[15,22]

Characteristically, the brain is atrophied asymmetrically in the posterior frontal and parietal lobes; both the pre- and post-central gyri are affected. Cortical atrophy is not usually as pronounced as in PiD. There is dilatation of the lateral ventricles and the striatum may be shrunken. The corticospinal tracts and corpus callosum may appear thinned. The substantia nigra appears pale in the majority of cases but there is not the brainstem atrophy typically found in patients with progressive supranuclear palsy (PSP).

The loss of neurons may be more severe in the outer cortical laminae and generate micro-vacuolation and reactive gliosis. Ballooned neurons are readily seen. They are found most frequently in the deeper cortical laminae (III, V and VI) and occasionally in subcortical areas, but may be absent in the most severely affected cortical areas. As in PiD, swollen neurons contain

epitopes of ubiquitin, neurofilament, and tau, but they are best demonstrated by αB-crystallin immunohistochemistry.[23] Ultrastructurally, swollen neurons contain 10–15 nm filaments and a smaller number of thicker 25–30 nm filaments, granular material and lipofuscin.[24] There is usually severe neuronal loss and accompanying astrocytosis in the substantia nigra. A characteristic feature is the intraneuronal basophilic inclusion. These 'corticobasal inclusions' are argyrophilic and fibrillar and are labeled by anti-ubiquitin and anti-tau antibodies (Fig. 12.6). Histologically, they resemble the neurofibrillary tangles (NFTs) of PSP. Ultrastructurally, the filaments of the inclusions are mainly straight with a diameter of 15 nm.[24] Similar inclusions may be found in the locus coeruleus and other brainstem nuclei. In addition to these corticobasal inclusions, small neuronal tau-positive inclusions and neuropil threads can be found in the superficial layers of the cortex.

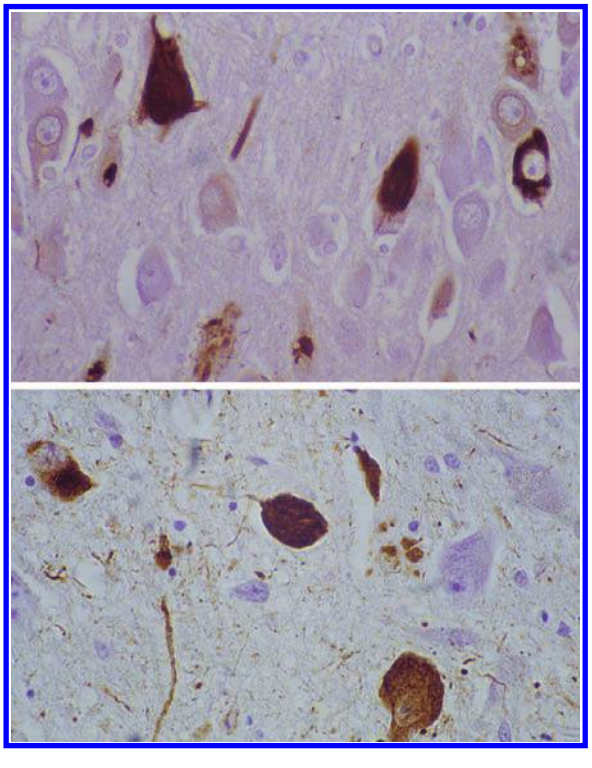

Fig. 12.6 Corticobasal degeneration. Neurofibrillary tangles in the CA1 subfield of the hippocampus (upper panel) and subthalamic nucleus (lower panel). Tau immunohistochemistry.

A striking feature of CBD is glial pathology in the affected areas. Filamentous argyrophilic structures are seen most commonly in astrocytes and less frequently in oligodendrocytes. Clusters of astrocytic tangles may form astrocytic plaques (Fig. 12.7). The inclusions in oligodendrocytes are argyrophilic fibrillar structures. Both the astrocytic and oligodendroglial inclusions in CBD are labeled by anti-ubiquitin and anti-tau antibodies. They are not recognized by α-synuclein antibodies, the major component of the glial cytoplasmic inclusions (GCIs) of multiple system atrophy (MSA).[25] Although it has been suggested that the GCIs are not specific to MSA and are also found in CBD and PSP, the oligodendroglial inclusions of CBD are morphologically and immunohistochemically different from the GCIs of MSA. The tau protein in CBD is predominantly 4R tau, which is different from that of both AD and PiD.

PROGRESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy (PSP) was first defined as a clinical and neuropathological entity in 1964 by Steele, Richardson, and Olszewski. Approximately 4% of parkinsonian patients have PSP, or 4 cases per million per year. The age at onset is around 60 years, an average duration of 6 years, and a slight male preponderance; the

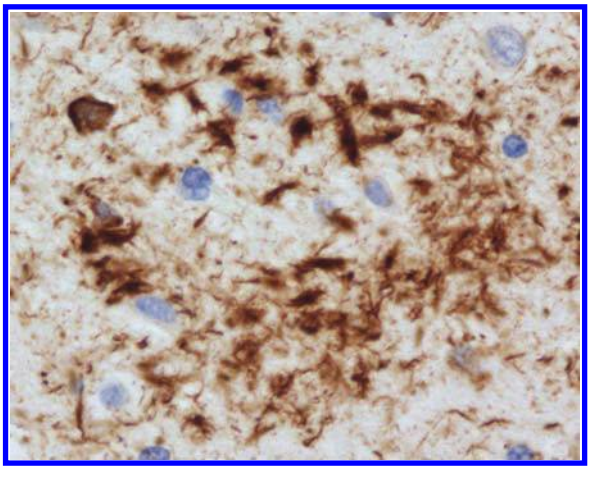

Fig. 12.7 Corticobasal degeneration. An astrocytic plaque in the superior temporal gyrus. Tau immunohistochemistry.

ratio of males to females is 60% to 40%. The clinical features include parkinsonism, vertical supranuclear gaze palsy, cognitive impairment consistent with FTD, dysarthria and dysphasia. Frontal lobe signs may be prominent.[26] The parkinsonian symptoms include bradykinesia, rigidity, gait disorder, masked fascies, neck dystonia and falls, but there is no tremor and the patient does not respond to levodopa. The disease is sporadic although rare autosomal dominant familial cases have been reported. Some familial cases with a PSP phenotype have *tau* mutations and these have been reassigned to FTDP-17; however, some familial cases of PSP fail to show mutations in *tau*.[27] The more common haplotype (H1) is significantly overrepresented in patients with PSP, extending earlier reports of an association between an intronic dinucleotide polymorphism and PSP.[15]

Macroscopically, the brain may appear normal or atrophied. The atrophy may include the globus pallidus, thalamus, subthalamic nucleus (Fig. 12.8) and, occasionally, the brainstem and cerebellum. The substantia nigra and locus coeruleus often appear pale. Histology reveals NFTs, neuropil threads, glial inclusions, neuronal loss and astrocytosis.[28] The predominant hallmark of PSP is the NFT (Fig. 12.9). They are found in the substantia nigra, globus pallidus, subthalamic nucleus, nucleus basalis of Meynert, pretectal area, tegmentum of the midbrain and pons, locus coeruleus, raphe nuclei, and the nuclei of various cranial nerves. The tangles are readily seen by silver impregnation methods but are best visualized by tau immunohistochemistry. Electron microscopy demonstrates that the tangles contain straight filaments of 12–15 nm,[29] which in turn are composed of six or more protofilaments of 2–5 nm.[30] Paired helical filaments (PHFs) and intermediate forms may be seen. Many astrocytes show inclusions, so-called astrocytic tangles, and tuft-shaped or thorn-shaped astrocytes have also been observed. Oligodendrocytes may also contain tau-positive inclusions called coiled bodies, which are different from the glial cytoplasmic inclusions of MSA. Predominantly 4R tau isoforms are present in PSP.[20]

The diagnosis is based on a semiquantitative assessment of the distribution of NFTs. The criteria also take into account the presence of neuropil threads and tau-positive astrocytes. Based on neuropathological criteria, three types of PSP can be distinguished: typical, atypical and combined.[31] Typical cases show the pathological features as originally described, while atypical cases are variants of the histological changes characteristic of PSP. In combined cases, in addition to PSP there is another disease process such as AD or vascular disease.

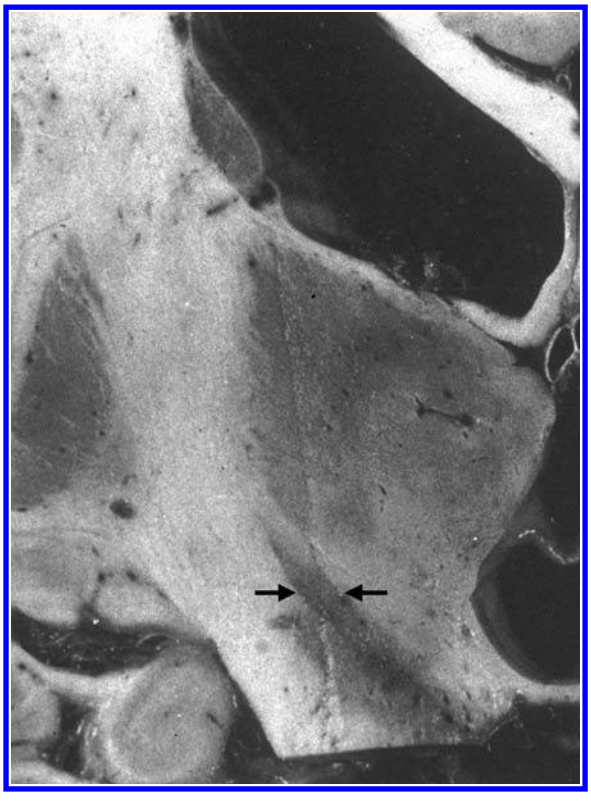

Fig. 12.8 Atrophy of the subthalamic nucleus (between arrows) in progressive supranuclear palsy.

NEUROFIBRILLARY TANGLE DEMENTIA

Senile dementia with tangles was first described by Ulrich et al.,[32] later called neurofibrillary predominant form of senile dementia,[33,34] and defined a subset of dementia cases with diffuse cerebral atrophy and predominant neurofibrillary tangles in the medial temporal lobe but without the signature β-amyloid and neuritic plaques of AD. The incidence of this disease in

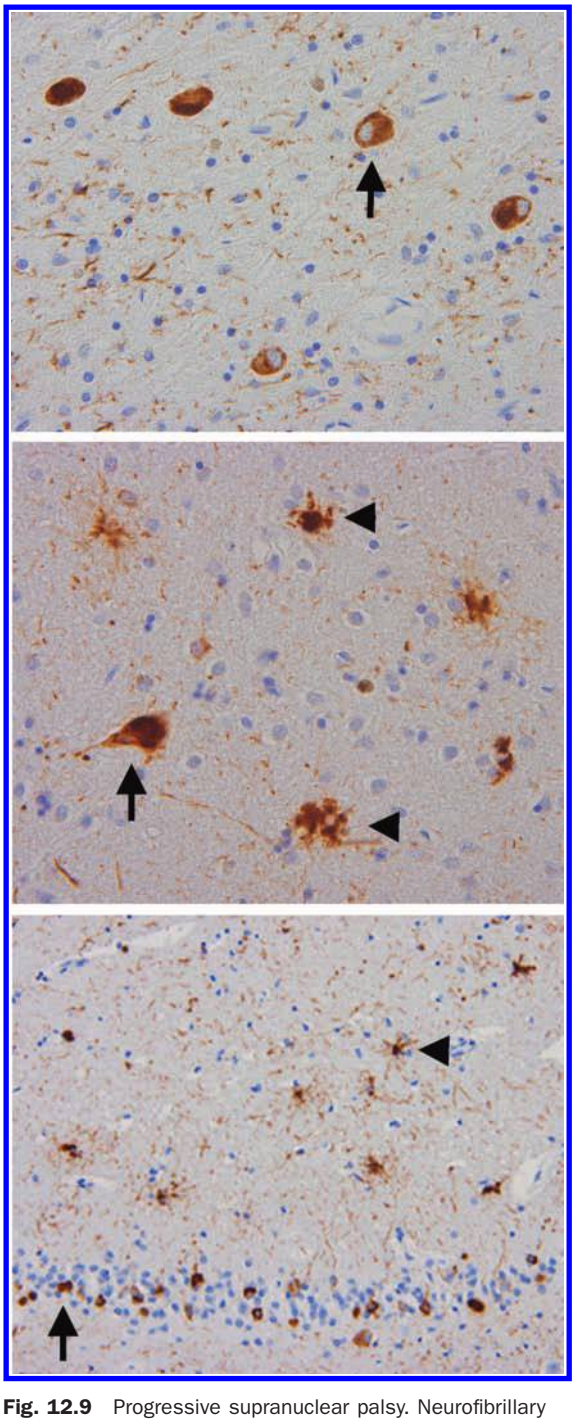

Fig. 12.9 Progressive supranuclear palsy. Neurofibrillary tangle (NFT; arrow) in the subthalamic nucleus (upper panel), a NFT (arrow) and thorny astrocytes (arrowheads) in the globus pallidus (middle panel), and small annular and globose NFTs (arrow) in the granule neurons of the dentate fascia and thorny astrocytes (arrowhead) in the molecular layer of the hippocampus (lower panel). Tau immunohistochemistry.

autopsy series is about 5%.[9,34] Early reports showed that more females than males were affected with a ratio of 3–4:1. The age at death in early studies ranges from 86 to 102 years with a duration of 1 to 5 years (mean = 4 years).[34] Clinically, most cases have dementia of the Alzheimer's type athough some patients have additional extrapyramidal signs. More recently, this neuropathologic entity has been observed in patients with FTD where it has been called neurofibrillary tangle dementia (NTD).[2]

Macroscopically, the brain may show mild to severe atrophy. Microscopically, there is neuronal loss, reactive gliosis, and frequent neurofibrillary tangles (NFTs) and neuropil threads (NTs) in the entorhinal cortex and parahippocampal gyrus (Fig. 12.10). The pyramidal neurons are typically affected in the entorhinal cortex, hippocampus, subiculum, amygdala, and adjacent cortex. In affected neocortex, NFTs may be seen readily in laminae III and V (Fig. 12.10). Both neuronal cytoplasmic tangles and extracellular 'ghost' tangles may be seen in the entorhinal cortex and hippocampus. Lower densities of NFTs and NTs may be observed in the frontal, temporal, and parietal neocortices. Argyrophilic grains (see below) have been seen in 20% to 66% of cases.[33–35]

Morphologically, ultrastructurally, and immunohistochemically, the NFTs of neurofibrillary tangle dementia are indistinguishable

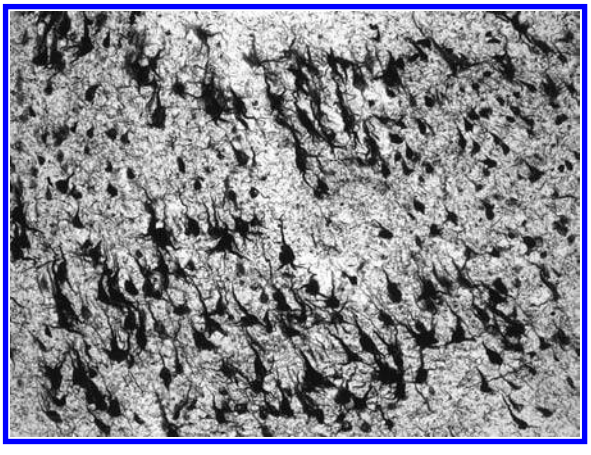

Fig. 12.10 Neurofibrillary tangle dementia. Bilaminar distribution of numerous neurofibrillary tangles in the parahippocampal gyrus. Gallyas silver impregnation.

from the NFTs of AD. The NFTs of NTD contain epitopes of hyperphosphorylated tau and biochemistry reveals that both 3R and 4R tau isoforms are present, similar to that seen in AD.

As the spectrum of tauopathies expands, NTD may be distinguished from AD by the absence of β-amyloid and neuritic plaques. Other tauopathies, including PSP, CBD, AGD, and FTDP-17, may be distinguished by the relative absence of neuronal and glial tau inclusions in subcortical nuclei and white matter in NTD. A rare, slowly progressive, early-onset dementia, which most closely resembles NTD, is diffuse neurofibrillary tangles with calcification (DNTC).[35] This disorder has been reported in Japan and has an early onset around 50 years with a duration of about 10 years. Clinically, these patients display personality and behavioral disturbances, language impairment, and often parkinsonism. As with NTD, there are NFTs in the medial temporal lobe, but their distribution is more widespread involving neocortex and subcortical nuclei in DNTC. Unlike NTD and other tauopathies, there is pronounced calcification in the globus pallidus in DNTC. The relationship between these two seemingly related disorders is unknown.

ARGYROPHILIC GRAIN DISEASE

Braak and Braak first described argyrophilic grains in a cohort of cognitively unimpaired aged subjects and dementia cases with no, or only sparse, AD-type pathology.[36,37] The disease is characterized by frequent argyrophilic fusiform grains in neuronal processes, coiled bodies in oligodendrocytes, and argyrophilic inclusions in the cytoplasm and processes of some astrocytes. All of these inclusions contain phosphorylated tau (4R)[38,39] and are ubiquitinated. Argyrophilic grain disease (AGD) is a neurodegenerative disorder that occurs, typically, in the brains of the elderly and affects 5% of all patients with dementia. Both men and women are affected and a major risk factor is advanced age.[36] Although AGD is predominantly a sporadic disease, there is one report of an autosomal dominant pattern of inheritance, San Francisco family A, with FTD, variable extrapyramidal symptoms, and prominent motor neuron disease, and with combined pathology of AGD and alpha-synuclein inclusions (Lewy bodies) in multiple areas.[40]

Macroscopically, most AGD cases are unremarkable, while some show atrophy of the frontal and temporal lobes. Unlike AD, there is little or no atrophy of the hippocampus or amygdala. However, the medial temporal lobe and the ambient gyrus may be atrophied in some cases.[41] Microscopically, argyrophilic grains may be detected in formalin-fixed paraffin wax-embedded tissue sections by silver impregnation methods and are best identified by the Gallyas method (Fig. 12.11). In silver impregnated sections, the grains appear as spindle-shaped structures and are seen most frequently in the entorhinal cortex, adjacent structures, and neighboring neocortex. Astrocytic inclusions and coiled bodies are not unique to AGD as they are also found in PSP and CBD. The presence of 4R tau-containing inclusions links AGD, PSP, and CBD. In addition to the lesions of AGD, AD-type pathology may also be present, especially in the medial temporal lobe. The absence of diffuse Aβ and neuritic plaques helps to distinguish AD-type changes from AGD.

FTD WITH PARKINSONISM LINKED TO CHROMOSOME 17 (FTDP-17)

In recent years, a number of families with FTD with and without movement disorder have been identified with mutations in the *tau* gene on chromosome 17. Although this group of disorders has been referred to as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) not all cases have parkinsonism. *Tau* gene mutations cause tau dysfunction by several mechanisms. Intronic and some exonic mutations affect the alternative splicing of exon 10 and consequently alter the relative proportions of 3R and 4R tau. Other exonic mutations impair the ability of tau to bind MTs and to promote MT assembly. Some mutations also promote the assembly of tau into pathological amyloid filaments. Intronic mutations clustered around the 5′ splice site of exon 10, as well as several mutations within exon 10, increase the ratio of 4R:3R tau by altering exon splicing.[42–45] As a result of these mutations there is a relative increase in

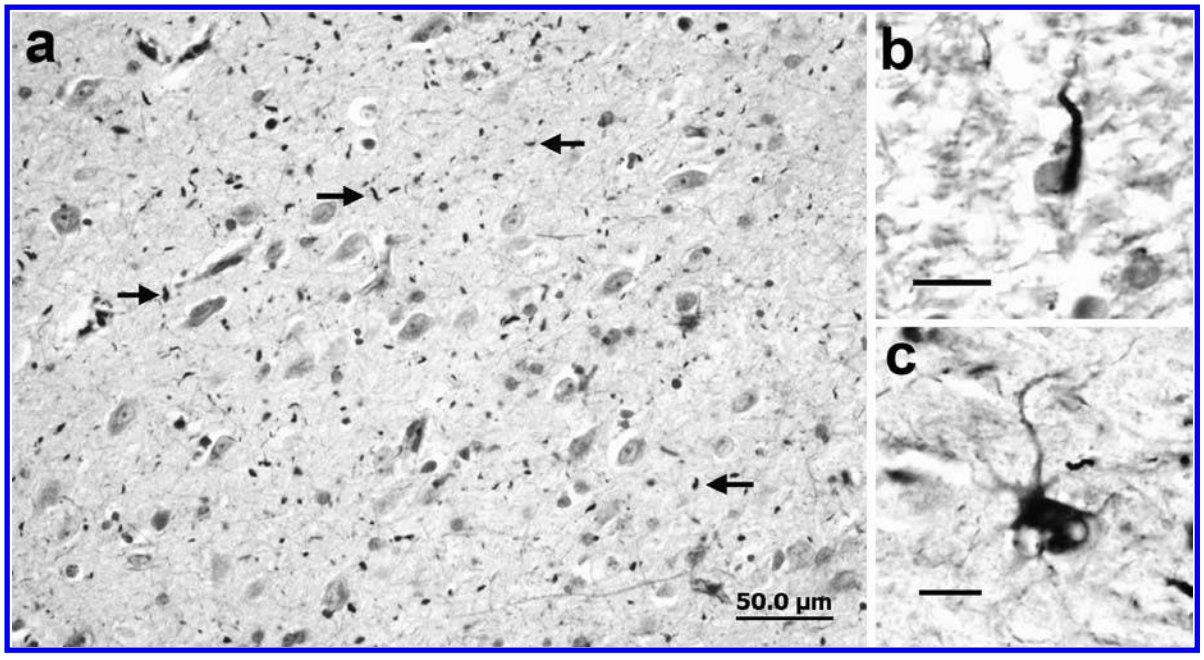

Fig. 12.11 Argyrophilic grain disease. (a) Argyrophilic grains (arrows) in the subiculum, (b) a coiled body in an oligodendrocyte, and (c) an astrocytic inclusion. Gallyas silver impregnation. Scale bars a = 50 µm, b and c = 10 µm.

mRNA containing exon 10. Biochemical analysis of insoluble tau extracted from FTDP-17 brain tissue reveals predominantly 4R tau isoforms (Fig. 12.3). Furthermore, 4R tau protein levels are increased in both affected and unaffected regions of FTDP-17 brains.[46–48]

These familial cases typically have atrophy of the frontal and temporal lobes (Fig. 12.12). Microscopically, neuronal loss, astrocytosis, microvacuolation, and swollen neurons are found in affected areas together with a spectrum of tau pathology including: intraneuronal NFT-like inclusions, neuronal globose tangle-like inclusions, intraneuronal Pick body-like inclusions, astrocytic tangle-like inclusions and oligodendroglial inclusions resembling coiled bodies and dystrophic neurites (Fig. 12.13). In a subset of cases with *tau* mutations, there may be sufficient NFTs and β-amyloid plaques to fulfil the neuropathological criteria for AD, but these cases, in addition to the *tau* mutation, may also have an apolipoprotein E ε4 allele.[49,49a] Mutations in the *tau* gene generate a heterogeneous biochemical phenotype: mutations may generate predominantly either 3R or 4R tau or a combination of the two (see Table 12.2). Thus, an extraordinarily wide range of tau pathology has been observed in these familial cases.

Although there is clinical and neuropathological overlap between the neurodegenerative tauopathies, each can be distinguished with variable probability by the distribution, severity,

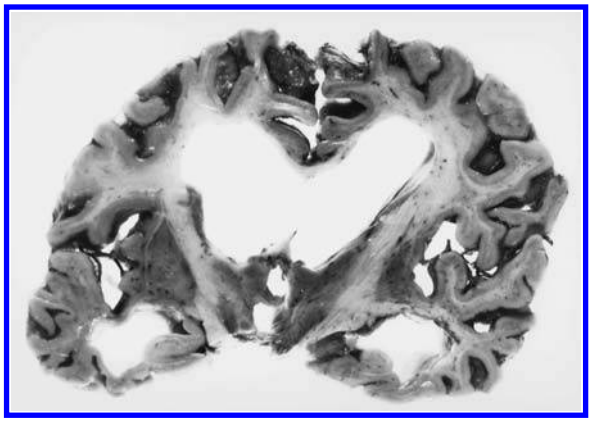

Fig. 12.12 FTDP-17. Atrophy of the frontal and temporal lobes at the level of the red nucleus in a case with intron tau 10+16 mutation.

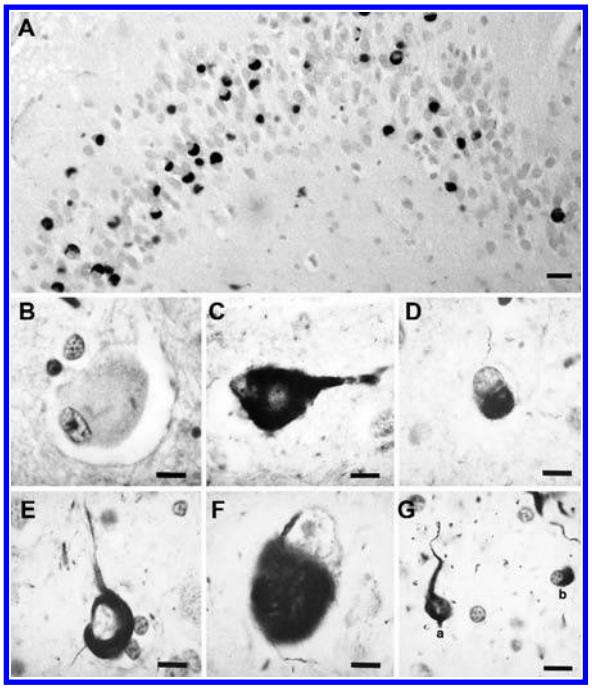

Fig. 12.13 Spectrum of neuronal and glial tau inclusions in FTDP-17. Inclusions in tau G389R mutation (A) and intron tau 10+16 mutation (B–G). (A) Numerous Pick body-like inclusions in the granule neurons of the dentate fascia. (C) A swollen achromatic neuron (hematoxylin and eosin). (B) A swollen neuron with a central area of pale anti-tau immunoreactivity surrounded by more intense staining. (D) An intraneuronal inclusion resembling a Pick body in the frontal lobe. (E) A neurofibrillary tangle-like inclusion in a pyramidal neuron of the frontal lobe. (F) A globose neurofibrillary tangle-like inclusion in the dorsal raphe nucleus. (G) An astrocytic fibrillary inclusion (a) and a coiled body (b) in an oligodendrocyte in the white matter of the frontal lobe. (B–F) Tau immunohistochemistry. Scale bars = 10 μm.

and morphology of tau-positive inclusions. In cases with a *tau* gene mutation, in addition to extensive neuronal loss and astrocytosis, tau-positive neuronal and glial inclusions may resemble those seen in AD, PSP, CBD, AGD, and PiD. This neuropathological heterogeneity is a striking feature of FTDP-17 and it is complemented by biochemical heterogeneity where there is variation in the proportions of tau isoforms, not only with different mutations, but also within the same brain.

FTLDs WITHOUT TAU INCLUSIONS

Amongst the neurodegenerative diseases, the FTLDs are neuropathologically strikingly heterogeneous. This pathological heterogeneity may be explained, in part, by different genetic loci in familial FTLDs. In addition to over 30 mutations in the *tau* gene that have been identified in cases of FTDP-17 (Table 12.2), extensive sequencing of *tau* in familial FTD cases with and without abnormal tau inclusions excludes *tau* as the genetic locus in those cases. Molecular genetic studies have linked familial FTLDs to loci on chromosomes 3, 9, and 17 (Table 12.1). Frontotemporal lobar degeneration in a Danish family has been linked to the centromeric region of chromosome 3 and mutations have been reported in the charged multivesicular body protein 2B gene (*CHMP2B*).[77] Conversely, the absence of any tau inclusions in familial FTLD may be associated with *tau* mutation; in one family with FTLD lacking tau- and ubiquitin-positive inclusions, and no insoluble tau detected by immunoblotting, sequence analysis revealed intronic tau 10+19 and +29 mutations.[50] Thus, FTLD like FTDP-17 is genetically heterogeneous.

(The neuropathology of FTLD and FTLD-MND-type, are described in Chapter 13.)

NEURONAL INTERMEDIATE FILAMENT INCLUSION DISEASE

Neuronal intermediate filament (IF) inclusion disease (NIFID) is a rare neurological disease with a clinically heterogeneous phenotype, including FTD, pyramidal and extrapyramidal signs, presenting at a young age.[9,78,79] In a series of 10 cases, the mean age at onset was 40 (range 23–56) years, the mean duration of disease was 4.5 (range 2.7–13) years, and the mean age at death was 45 (range 28–61) years.[9] Both sexes are affected, the ratio of men to women being 2:3. Although largely a sporadic disorder, one case has been reported where the father had parkinsonism and dementia indicating evidence of hereditability.[79] Presenting symptoms include: personality change, apathy, blunted affect, and disinhibition. There may also be memory loss, cognitive impairment, and language deficits in

Table 12.2 *Tau* mutations in FTDP-17

*Protein mutation**	*Region*	*Effect on exon 10 splicing*	*Effect on MT assembly*	*Pathological phenotype*	*References*
R5H	Exon 1	No	Yes	FTDP-17	(51)
R5L	Exon 1	No	Yes	PSP-like	(52)
K257T	Exon 9	ND	Yes	PiD-like	(53,54)
I260V	Exon 9	No	Yes	FTDP-17	(55)
L266V	Exon 9	4R ↑	Yes	PiD-like	(56)
G272V	Exon 9	ND	Yes	FTDP-17	(42)
E9+33	Intron 9	ND	ND	ND	(57)
N279K	Exon 10	4R ↑	No	PSP-like	(58)
ΔK280	Exon 10	3R ↑	Yes	FTDP-17	(57)
L284L	Exon 10	4R ↑	No	AD-like	(43)
N296N	Exon 10	4R ↑	Yes	CBD-like	(59)
N296H	Exon 10	4R ↑	Yes	FTDP-17	(60)
ΔN296	Exon 10	4R ↑	No	PSP-like	(61)
P301L	Exon 10	No	Yes	FTDP-17	(42)
P301S	Exon 10	No	Yes	CBD-like, FTDP-17	(62,63)
S305N	Exon 10	4R ↑	Yes	CBD-like	(64) (65)
S305S	Exon 10	4R ↑	No	PSP-like	(66)
E10+3	Intron 10	4R ↑	No	FTDP-17	(46)
E10+11	Intron 10	4R ↑	No	FTDP-17	(67)
E10+12	Intron 10	4R ↑	No	FTDP-17	(68)
E10+13	Intron 10	4R ↑	No	ND	(42)
E10+14	Intron 10	4R ↑	No	PSP-like, FTDP-17	(42)
E10+16	Intron 10	4R ↑	No	AD-, PiD-, PSP-, CBD-like, FTDP-17	(42)
E10+19	Intron 10	3R ↑	No	FTLD	(50)
E10+29	Intron 10	3R ↑	No	FTLD	(50)
L315R	Exon 11	ND	Yes	PiD-like	(69)
S320F	Exon 11	ND	Yes	PiD-like	(70)
Q336R	Exon 12	ND	Yes	PiD-like	(71)
V337M	Exon 12	ND	Yes	FTDP-17	(72)
E342V	Exon 12	4R ↑	ND	FTDP-17	(73)
S352L	Exon 12	ND	Yes	Atypical	(74)
K369I	Exon 12	ND	Yes	PiD-like	(75)
G389R c2170G>C	Exon 13	ND	Yes	PiD-like	(76)
G389R c2170G>A	Exon 13	No	Yes	PiD-like	(53)
R406W	Exon 13	ND	Yes	PSP-like	(42)

* Protein mutation name relative to the longest human adult tau isoform; four microtubule binding repeats (4R) and two inserts (2N); MT, microtubule; Δ, deletion; 4R ↑, increase in the ratio of 4R:3R tau isoforms; ND, not determined.

half of the cases. Motor weakness may be evident at presentation in a minority of patients. Extrapyramidal features are present in most cases, and less frequently buccofacial apraxia and supranuclear ophthalmoplegia. Hyperreflexia is a common finding and most patients became mute with advanced disease. Structural brain imaging and macroscopy typically show atrophy of the frontal and temporal lobes and the caudate nucleus.

In all cases, there is variable atrophy of subcortical nuclei including the basal ganglia,

amygdala, hippocampus, and thalamus. The brainstem, cerebellum, and spinal cord appear unremarkable. In the more severely affected cases the cortical ribbon is thinned. The histological changes include the stereotypic lesions of FTLDs: neuronal loss, status spongiosus, and gliosis in temporal and frontal isocortex. Swollen achromatic neurons are also seen. However, the most striking feature is the presence of inclusions containing neuronal IF proteins, i.e. the neurofilament (NF) triplet proteins and α-internexin (Fig. 12.14). The severity of each of these histological abnormalities varies from case to case.

Microscopy reveals extensive neuronal loss and reactive astrocytosis in the frontal, medial temporal, and parietal lobes, and varying degrees of loss in subcortical nuclei including the caudate nucleus, putamen, globus pallidus, amygdala, substantia nigra and locus coeruleus. A variable degree of neuronal loss and axonal swellings may be present in the cerebellum.

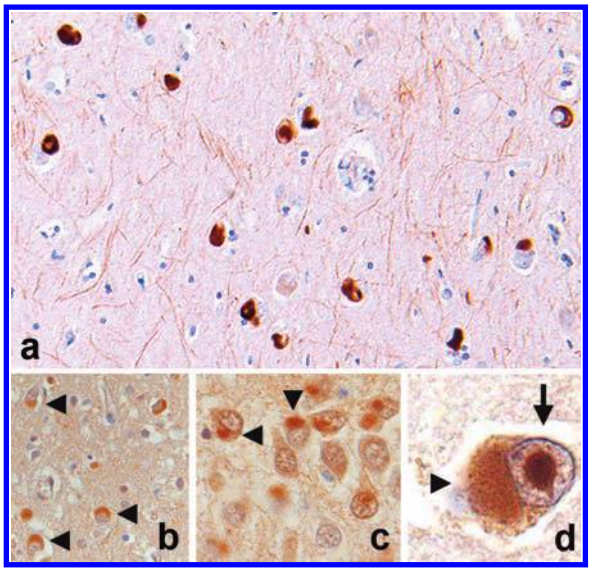

Fig. 12.14 Neuronal inclusions in NIFID are pleomorphic and may be seen in the same section with normal axons which also contain neuronal IFs (a). α-Internexin immunohistochemistry. Neuronal inclusions in NIFID are variably ubiquitinated: inclusions (arrowheads) in the frontal lobe (b) and granule cells of the dentate gyrus (c). A neuronal cytoplasmic (arrowhead) and intranuclear inclusion (arrow) are present in the same neuron (d). (b–d) Ubiquitin immunohistochemistry.

Occasional swollen achromatic neurons are observed in affected areas. In areas of neuronal loss, faintly eosinophilic, intraneuronal, cytoplasmic inclusions are present. In hematoxylin and eosin-stained sections, hyaline aggregates of neuronal IFs are observed. The inclusions are variably argyrophilic with modified Bielschowsky and Bodian silver impregnations and superficially resemble the Pick bodies of PiD. Immunohistochemistry demonstrates the presence within the inclusions of all class IV IF proteins (NF-H, NF-M, NF-L, and α-internexin). The morphology of the inclusions is extremely variable throughout the neuraxis. Axonal swellings, similar to those found in amyotrophic lateral sclerosis and normal aging, but which are not specific to any neurodegenerative disease, are also seen in affected areas and in underlying white matter, corticospinal tracts and other white matter tracts. In cases with pyramidal signs, there may be evidence of corticospinal tract degeneration in the spinal cord. However, motor neurons in the anterior horns are relatively spared and the number of pyknotic neurons is much lower than that typically seen in classical MND.

The cytoplasmic inclusions of NIFID are variably ubiquitinated, as demonstrated by immunohistochemistry. Ubiquitinated and neuronal IF-positive inclusions are most numerous in the youngest cases.[9] Ubiquitinated inclusions are found in cortex and subcortical nuclei and in the neurons of the dentate gyrus in all cases where they resemble those seen in FTLD-MND-type. Rare single (Fig. 12.14d) and multiple round and elongated intranuclear inclusions may also be observed in neurons containing cytoplasmic inclusions. The intranuclear inclusions in NIFID are not labeled by anti-neuronal IF antibodies.

Ultrastructural study of the neuronal cytoplasmic inclusions in NIFID, like those of other inclusions in FTLDs, reveals aggregates of granular filamentous material with no apparent limiting membrane. The granular material resembles the morphology of ribosomes and the filaments have an apparent diameter of 10–25 nm. Immunoelectron microscopy demonstrates that the filaments of the inclusions contain epitopes of neuronal IF proteins.[9]

BASOPHILIC INCLUSION BODY DISEASE

Rare cases of basophilic inclusion body disease (BIBD) may present as juvenile,[80,81] or adult-onset MND,[82,83] FTD,[10,84] or a combination of both.[85] Typically, patients are younger when symptoms develop (29–30 years[10] and 52–58 years[86]) than those with PiD. Features of MND and FTD are comparable to the heterogeneous phenotype of NIFID. The early age at onset of this widespread but rare disease hints at a genetic cause, but none has been identified.

Cases typically show pronounced atrophy of the frontal and temporal lobes with less involvement of the parietal lobe. Coronal slices reveal marked atrophy of the striatum, often with a thinned caudate nucleus, thalamus, and amygdala. The substantia nigra is also depigmented. Microscopy shows the stereotypic features of all FTLDs. The histological hallmark of this disease is the basophilic inclusion body[10] which does not contain tau, or α-synuclein, or neuronal IF proteins (Fig. 12.15). Basophilic inclusion bodies are found in affected neocortex preferentially affecting the superficial laminae similar to the distribution in Pick's disease.[87]

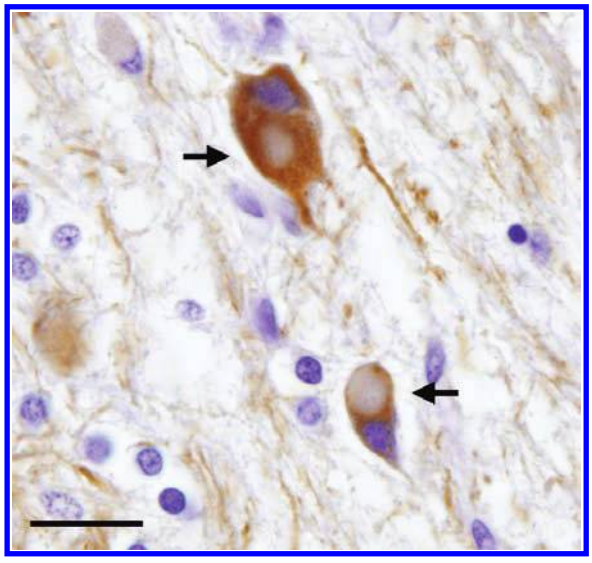

Fig. 12.15 Neuronal cytoplasmic inclusions in the pons of BIBD. The inclusions (arrows) are outlined, but not labeled, by anti-neuronal IF protein antibodies. α-Internexin immunohistochemistry. Scale bar = 10 μm.

Unlike Pick bodies in PiD, basophilic inclusion bodies are not usually found in the hippocampus and dentate gyrus. However, inclusions are found in subcortical nuclei including the putamen, caudate nucleus, globus pallidus, nucleus basalis of Meynert, red nucleus, subthalamic nucleus, periaqueductal gray and in the anterior horns of the spinal cord. Unlike in MND, no Bunina bodies and no ubiquitin-positive, skein-like inclusions are seen in cases of BIBD. The inclusions are variably basophilic, and occasionally eosinophilic, in hematoxylin and eosin-stained sections. The inclusions are variably ubiquitinated and contain variable amounts of RNA as shown by acridine orange staining. Misfolded proteins seen in tauopathies, synucleinopathies, and neuronal IF proteins are absent from these inclusions (Fig. 12.15). Electron microscopy shows that the inclusions are not membrane-bound and contain fibrils with a diameter between 13 and 25 nm and variably granular in appearance.[10] Swollen axons and axonal spheroids are also present, but these are not specific to BIBD, as they are commonly seen in other neurodegenerative diseases and normal aging.

FTD WITH INCLUSION BODY MYOPATHY AND PAGET'S DISEASE

Hereditary inclusion body myopathy (IBM) associated with Paget's disease of bone (PDG) and early-onset FTD is a rare, lethal, autosomal dominant progressive disease that is linked to chromosome 9.[88] The disease features adult-onset proximal and distal muscle weakness, early-onset PDB and, in most cases, FTD. The phenotypic variation in this disease is remarkable and death may precede overt clinical symptoms in one or more of the affected tissues. Thus, in 13 families in which mutations in *valosin-containing protein* (*VCP*) gene were reported, 82% had myopathy, 49% had PDB and 30% had early-onset FTD.[11] The mean age at presentation was 42 years for both IBM and PDB, whereas FTD typically developed somewhat later at age 53 years, possibly indicating greater functional reserve in brain tissue. Similar inclusions are seen in IBMPFD myopathic muscle and PDB osteoclasts, indicating common

pathogenetic mechanisms. Six missense mutations in *VCP* have been reported, resulting in the amino acid substitutions: R95G, R191Q, R155H, R155C, R155P, A232E.[11] Human VCP is a 644 amino acid protein encoded by a gene with 17 exons which maps to chromosome 9p13-p12. It is a member of the AAA-ATPase superfamily involved in vesicle transport and fusion, 26S proteasome function, and assembly of peroxisomes. VCP is a structural protein and is associated with the assembly of clathrin, and the heat-shock protein HSP70. VCP has been implicated in a number of cellular events that are regulated during mitosis, including membrane fusion and ubiquitin-dependent protein degradation. Ten of the 13 families with IBMPFD had an amino acid substitution at codon 155 in VCP and all were present within the N-terminal domain which is involved in ubiquitin binding,[89] indicating that mutations in this region may compromise the normal ubiquitin protein degradation pathway.

To date, few brains of patients with IBMPFD have been examined. Of those patients with FTD, the characteristic features of FTLD have been observed. The atrophy is less pronounced than in other FTLDs. The neuropathological hallmark lesions are neuronal ubiquitin-positive intranuclear inclusions and dystrophic neurites and rare cytoplasmic inclusions. A subset of intranuclear inclusions contains epitopes of VCP (Fig. 12.16). Large focal inclusions and smaller foci containing VCP are present in muscle fibers of patients with IBMPFD. This pattern of staining is not specific to IBMPFD as VCP aggregates are also seen in muscle fibers in sporadic IBM. Ubiquitin-positive, VCP-positive neuronal inclusions are seen in brain of affected patients. This immunoreactive profile of the inclusion bodies is not unique to IBMPFD because VCP has also been shown to be a component of a subset of inclusions in other neurodegenerative diseases, including expanded polyglutamine protein aggregates, dystrophic neurites of AD, α-synuclein aggregates in dementia with Lewy bodies (DLB), PD and multiple system atrophy (MSA), and ubiquitinated inclusions in MND.[90,91] Thus, the presence of VCP in the inclusions of IMBPFD implicates this protein in the pathogenesis of several protein-folding diseases.

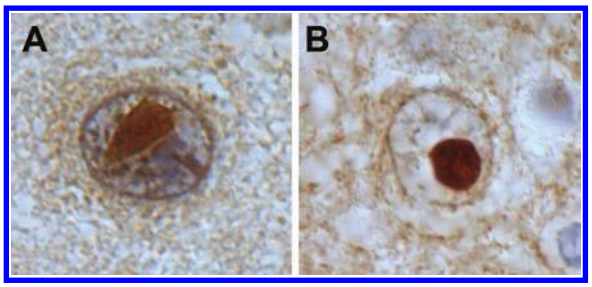

Fig. 12.16 Neuronal intranuclear inclusions in the temporal neocortex of a case of IBMPFD. (A and B) Ubiquitin and valosin-containing protein immunohistochemistry, respectively.

CONCLUSIONS

The accumulation of misfolded proteins in inclusion bodies is a common feature of a wide variety of sporadic and familial neurodegenerative disorders that present clinically with FTD. These diseases are distinguished by the distinct topographic and cell type-specific distribution of inclusions. The biochemical and ultrastructural characteristics of the inclusions also reveal a significant phenotypic overlap. The discovery of multiple mutations in the *tau* gene leading to abnormal filamentous inclusions demonstrates that tau dysfunction is sufficient to produce neurodegenerative disease. Experimental evidence indicates that mutations lead to specific alterations in expression, function, and biochemistry of tau proteins. Similarly, mutations in *VCP* result in impairment of ubiquitin degradation pathways, protein aggregation, inclusion formation, and neurodegeneration in a subset of cases with IBMPFD. The identification of additional gene mutations in the FTLDs or polymorphisms at distinct genetic loci that either cause disease, or are risk factors, will provide additional insights into disease pathogenesis as well as the development of novel strategies for treatment and prevention.

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13

Molecular and cellular neuropathology of cognitive dysfunction in ALS

Eileen H Bigio

BACKGROUND

Frontotemporal lobar degeneration with motor neuron disease (FTLD-MND), also called motor neuron disease dementia (MNDD) was first described in amyotrophic lateral sclerosis (ALS) subjects with cognitive impairment.[1,2] Later, it was observed in the absence of ALS, and in this case has been called frontotemporal lobar degeneration of the motor neuron disease type (FTLD-MND-type) or motor neuron disease inclusion dementia (MNDID).[3,4] Some are uncomfortable with terminology that includes 'motor neuron disease' when MND is not present, and use the term frontotemporal lobar degeneration with ubiquitinated inclusions (FTLD-U or FTLD-Ub). The current recommended terminology is FTLD-MND when ALS is present and FTLD-MND-type when ALS is absent.[5,6] All of these terms are rather long and awkward, but they do illustrate the overlapping nature of these disorders. Because of this overlap, and because the only difference between FTLD-MND and FTLD-MND-type is the presence or absence of clinical and pathologic ALS, this chapter discusses both FTLD-MND and FTLD-MND-type.

PATHOLOGY OF ALS

The pathology of ALS is that of both upper and lower motor neuron degeneration. Upper motor neuron pathology includes Betz cell loss and corticospinal tract (CST) degeneration (internal capsule, cerebral peduncles, pontine CSTs, pyramid, and spinal cord lateral and ventral CSTs). There are rare reports of Bunina bodies and ubiquitinated skein-like inclusions (SLIs) in upper motor neurons. Lower motor neuron pathology consists of neuronal loss and gliosis, chromatolysis, neuronophagia, hyaline inclusions, Bunina bodies, ubiquitin-positive SLIs and Lewy-like bodies (LLBs), axonal spheroids, a fragmented Golgi apparatus,[7] and ventral nerve root atrophy. Most of these are also found in brainstem motor neurons of the hypoglossal, ambiguus, facial, and trigeminal nuclei, but oculomotor, trochlear, and abducens nuclei seem to be spared.

Bunina bodies are composed of cystatin-C,[8] a cysteine protease inhibitor involved in the apoptotic pathway and present in normal neurons. SLIs[9,10] and LLBs may be composed of fragments of neurofilament,[11] although this is not completely clear. LLBs appear to be condensed SLIs;[12] on the other hand, LLBs appear to contain

peripherin while SLIs apparently do not.[13] There is one report showing co-localization of Bunina bodies and SLIs.[14]

PATHOLOGY OF FTLD-MND (MNDD) AND FTLD-MND-TYPE (MNDID, FTLD-U)

General: FTLD-shared pathology

The presence or absence of concomitant ALS is the only feature that differs between FTLD-MND-type (no ALS) and FTLD-MND (with ALS). The FTLD pathology present in both includes the general gross and microscopic features shared variably between all FTLDs, and specific immunohistochemical inclusions and deposits. Gross pathologic findings shared by FTLDs include circumscribed atrophy of frontal, temporal, and sometimes parietal lobes, atrophy of the caudate nucleus, and pallor of the substantia nigra (Fig. 13.1). Microscopically, FTLDs share superficial (cortical layer II) microvacuolation and gliosis (Fig. 13.2) in frontal, temporal, motor, and/or parietal lobes, and variable neuronal loss and gliosis in cortical layers III and V in the same cortical regions (56% F, 52% T, 49% P) as well as in the caudate, putamen, and substantia nigra.[15] Subicular neuronal loss and gliosis are also frequently present in FTLDs.[16] Pyramidal tract degeneration in FTLD-MND-type has been described,[17] as has fragmentation of the Golgi apparatus in lower motor neurons.[18] In FTLD-MND, pallidoluysian degeneration has also been reported.[19,20]

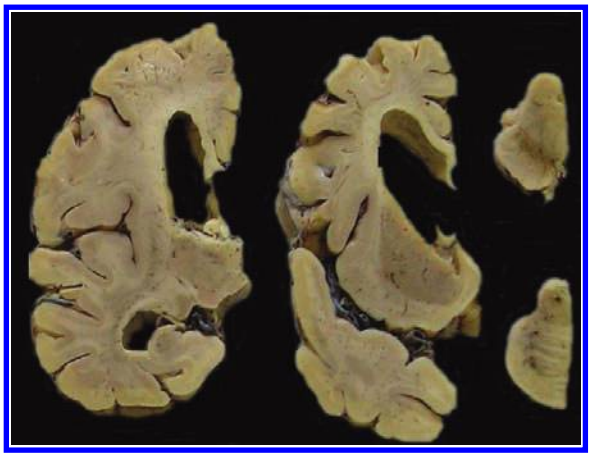


Fig. 13.1 Frontotemporal lobar degeneration: gross pathology variably shared by all FTLDs.

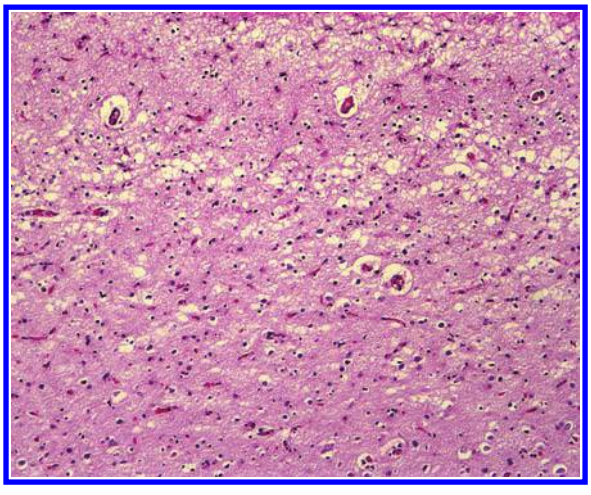
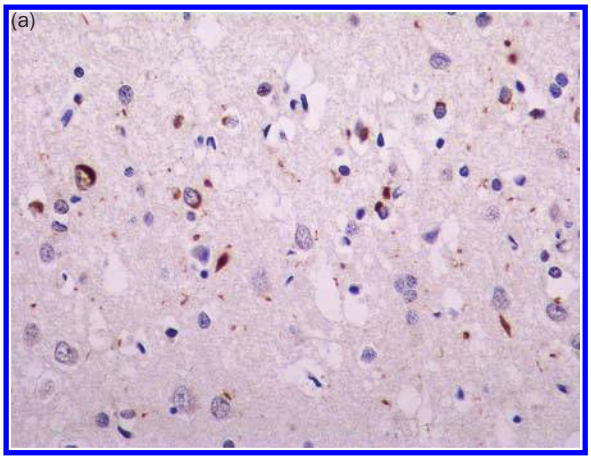
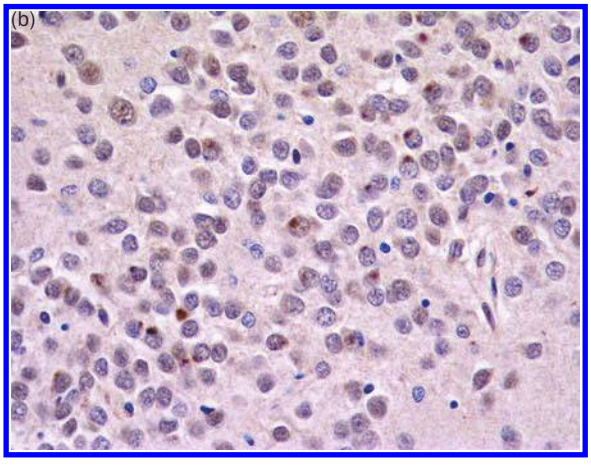


Fig. 13.2 Frontotemporal lobar degeneration: microscopic superficial microvacuolation, shared by all FTLDs.

FTLD-MND-type and FTLD-MND-specific pathology

The pathology specific to FTLD-MND and FTLD-MND-type consists of ubiquitin-positive, tau- and α-synuclein-negative cytoplasmic inclusions and dystrophic neurites in cortical layer II of frontal, temporal, motor, and/or parietal lobes, in the hippocampal dentate gyrus, and in the striatum (Fig. 13.3). Dystrophic neurites are sometimes also found in the neocortex in deeper layers, layers III and V. The cytoplasmic inclusions (CI) are rather pleomorphic, and may be round, reniform, crescent- and bar-shaped, circular, and granular, which may represent stages in their development. The dystrophic neurites (DN), which have also been called swollen axons, are thick and elongated. Intranuclear inclusions (INIs), seen more frequently in familial cases, and reported by some to be present in only familial cases,[21–25] are elongated, 'cigar-shaped', with a 'cat's eyes' appearance (Fig. 13.4). INI frequently distort the nucleus and are generally surrounded by a rim of nuclear clearing. When sectioned transversely, they appear to be round.





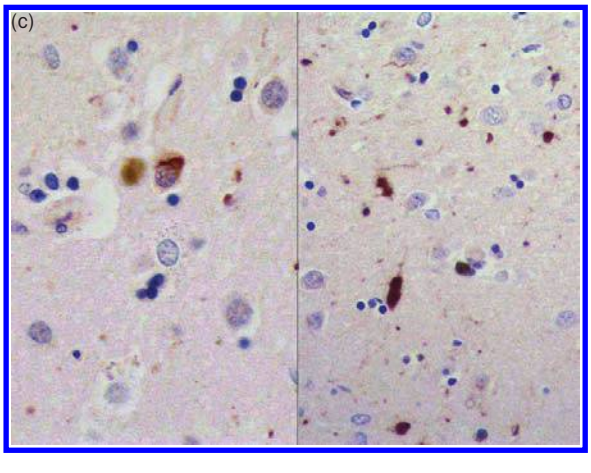


Fig. 13.3 Ubiquitinated insoluble deposits, tau- and α-synuclein negative, specific for FTLD-MND and FTLD-MND-type. (a) Frontal cytoplasmic inclusions and dystrophic neurites. (b) Dentate gyrus cytoplasmic inclusions. (c) Striatal cytoplasmic inclusion (left) and dystrophic neurites (right).

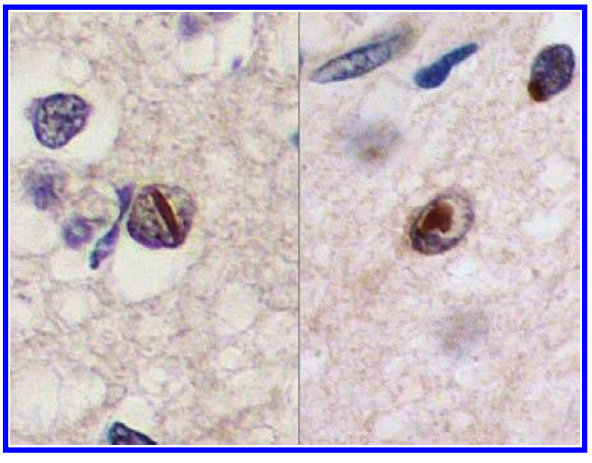


Fig. 13.4 Intranuclear ubiquitinated inclusions: longitudinal (left) and presumably cross-section (right).

Glial pathology is sometimes present, and appears to be best labeled with tau2, not at all with tau1, and a subset of which is stained inconsistently with AT8, PHF1, and tau5.[26] Glial pathology may be seen with Gallyas[27] (and personal observation) (Fig. 13.5), but in Forno's cases[26] Gallyas did not label the glial pathology.

Distribution and density of FTLD-MND-type and FTLD-MND-specific pathology

The distribution and density of CIs, DNs, and INIs is variable[21,28,29] (and unpublished data from study by Lipton et al.). Some cases have no

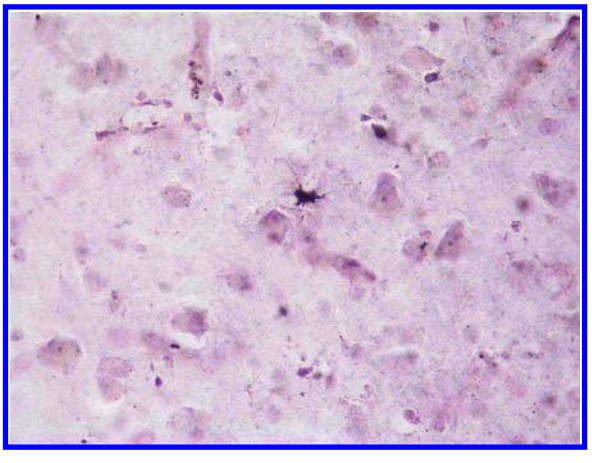


Fig. 13.5 Gallyas-positive glia in FTLD-MND.

dentate gyrus CIs, emphasizing the fact that the diagnosis of FTLD-MND or FTLD-MND-type should not be excluded on the basis of ubiquitin immunostains of the hippocampal region alone. In only approximately half (or less) of the cases do absent to sparse or moderate to frequent inclusions correlate between dentate gyrus and superficial frontal cortex (see Table 13.1). Kovari et al.[29] suggest that because in their study the density of dentate gyrus inclusions correlated negatively with the duration of illness, they may be associated with a more aggressive form of the disease.

Pathology of Northwestern ALS/FTLD-MND cases

At present, we have 76 cases of ALS in our files, 26 of which are familial. Five of the familial cases have SOD1 mutations – four with exon 1 A4V and one with exon 4 G85R. Twenty-three of the 76 ALS cases have FTLD-MND; none of these have SOD1 mutations. Fourteen of the 23 FTLD-MND subjects were demented, 8 were not, and one is unknown. What is the significance of FTLD-MND pathology without clinical dementia? The answer is not clear. Of course, it could mean that there was no FTD, or that potential FTD was not investigated in the setting of a fatal physical disorder. If there was no FTD, is the FTLD-MND pathology specific for FTD? If not, what does the FTLD-MND-type pathology mean in the ALS cases? It is likely, however, that neuropsychologic testing would have revealed more FTD, or cognitive dysfunction, than was recognized in this group. In one paper, when 100 ALS patients were evaluated neuropsychologically, 23 met criteria for FTD.[30] Conversely, FTD sometimes precedes motor symptoms in ALS, and up to 15% of FTD patients can be expected to develop ALS.[30,31] Additionally, pathologic features of ALS may be present in FTLD-MND-type cases in the absence of motor symptoms.[32]

Pathology of Northwestern FTLD-MND and FTLD-MND-type cases

Lipton et al. recently reported FTLD-MND and FTLD-MND-type to be most common (29 cases) in their series of 76 FTLDs from UT Southwestern,[33] and Josephs et al. reported it to be the most common (18 cases of what they call FTLD-U) in their series of 29 FTLDs from the Mayo Clinic.[28] We currently have 66 FTLDs at Northwestern, 40 of which are FTLD-MND or FTLD-MND-type. It is becoming increasingly clear that FTLD-MND and FTLD-MND-type are the most common FTLD subtype(s). Diagnoses in the remaining 26 Northwestern FTLD cases are 8 cases of CBGD, 7 PSP cases, 3 Pick disease, one FTDP-17 with the L266V tau mutation and Pick-like pathology, 3 unclassifiable tauopathies, 2 tangle-predominant senile dementia cases, one hippocampal sclerosis only case, and one case of dementia lacking distinctive histology (DLDH). Interestingly, the one DLDH case in our files is an ALS case.

Of our 40 FTLD-MND and FTLD-MND-type cases, 23 have FTLD-MND or FTLD-MND pathology. Fifteen of our 23 FTLD-MND or FTLD-MND pathology cases are familial, and 3 of these have INIs (discussed above). Of the 17 FTLD-MND-type cases, 9 are familial, 7 of these

Table 13.1 Correlation between dentate gyrus and frontal cortex inclusions*

Dentate gyrus and frontal cortex estimates of severity	*Bigio et al.*[21] *number of cases*	*Lipton et al.*[33] *number of cases*
Dentate and frontal both absent to mild	7	4
Dentate absent to mild/frontal moderate to severe	5	7
Dentate moderate to severe/frontal absent to mild	17	6
Dentate and frontal both moderate to severe	3	5

*Adapted from Bigio et al.[21] and Lipton et al.[33]

have INIs, and there are INIs in 4 cases that are apparently not familial. However, the mother of one of these patients, whose onset was at age 62, died at age 56 of hepatic carcinoma, possibly before she might have developed symptoms, and the father of another left the family to return to his native Scotland and subsequent history for him is unknown. We are aware that a negative family history must always be interpreted with caution, because in self-reported family histories there may be missing or incorrect information, and the issue of paternity may always be raised.

In 37 of the 40 cases, the pathology is that of typical FTLD-MND or FTLD-MND-type as described above. In 3 of the 15 familial cases, however, many of the ubiquitinated cytoplasmic inclusions in frontal and motor cortex are in deeper cortical layers rather than cortical layer II (Fig. 13.6). α-Synuclein stains of these cases were negative. None had SOD1 mutations. This variation in the pathology of FTLD-MND is at this point of uncertain significance.

Familial and sporadic cases – do INIs signify familial disease?

Woulfe et al., in their 2001 paper describing INIs in dementia of the motor neuron disease type, found INIs in 3 of their 12 cases.[25] These three were familial. Two familial cases did not have INIs. Mackenzie and Feldman, in two recent papers,[22,23] describe INIs in six FTLD-MND-type and one FTLD-MND cases, all familial. Six familial cases had no INIs. We found INIs[21] in 11 cases, 9 of which were familial (we currently have 14 cases with INIs, 10 familial). Eleven familial cases had no INIs (currently 14). While we need to stress the caveats regarding interpretation of a negative family history, statistically, in our series and using current numbers of combined FTLD-MND and MND-type cases, INIs do not seem to correlate with a positive family history (p = 0.33, Fisher's exact test). Looking at the groups separately does not improve the statistics (FTLD-MND-type, p = 0.13, FTLD-MND, p = 0.53, Fisher's exact test). In other words, while a positive family history is more likely when INIs are present, their absence does not make a positive family less likely. Curiously, however, in ALS cases, FTLD-MND or FTLD-MND pathology was present in 15 of 26 ALS cases with and 9 of 50 cases without a positive family history, suggesting that FTLD-MND or FTLD-MND pathology is present in familial ALS (p = 0.0007, Fisher's exact test).

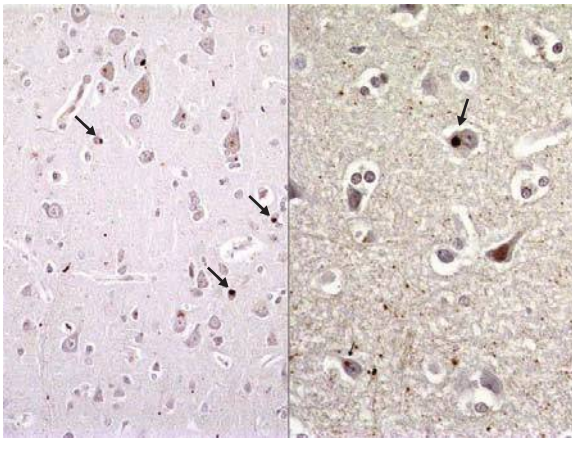


Fig. 13.6 Ubiquitinated cytoplasmic inclusions (arrows) in cortical layers III (left) and V (right) in FTLD-MND.

GENETICS OF FTLD-MND AND FTLD-MND-TYPE

No specific mutation has been identified to date in families affected by FTLD-MND or MND-type. Some familial cases have shown linkage to chromosome 17,[24,34,35] but no tau mutations have been identified as yet. Additionally, ubiquitinated inclusions have been observed in some of the familial FTD-ALS cases showing linkage to chromosome 9[36] (Fig. 13.7). And last, a balanced translocation was recently described in an apparently sporadic FTD-ALS case.[37] Interestingly, the chromosome 21 breakpoint of this translocation, t(18;21)(q23;q22), is in the region of the SOD1 locus. Knowing the mutation in familial cases might allow identification of the protein comprising the inclusions in both familial and sporadic cases, which so far has been elusive.

MOLECULAR STUDIES IN FTLD-MND AND FTLD-MND-TYPE

Arai et al.[38] recently demonstrated the immunohistochemical presence of p62 in ubiquitinated

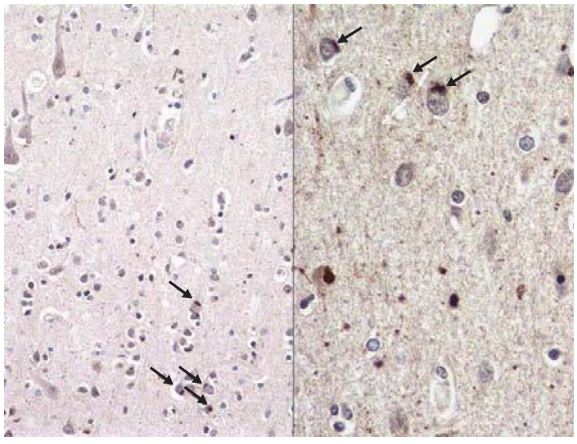


Fig. 13.7 Ubiquitinated cytoplasmic inclusions (arrows) in cortical layers III (left) and V (right) in FTD-ALS linked to chromosome 9.

neuronal inclusions in five of five FTLD-MND-type cases, and absence of tau, α-synuclein, NF, MAP5, heparan sulfate, Cu/Zn superoxide dismutase, αB-crystallin, HSP70, and GFAP. p62 is a ligand for the Src homology 2 domain of $p56^{lck}$ (lymphoid-specific Src family tyrosine kinase), and can bind noncovalently to ubiquitin and several signaling proteins that lead to activation of NF-κB. Since p62 has also been found in several other inclusions (neurofibrillary tangles (NFTs) in Alzheimer disease, Pick bodies in Pick disease, glial inclusions in progressive supranuclear palsy and cortical-basal ganglionic degeneration, Lewy bodies in Parkinson disease, glial cytoplasmic inclusions in multiple systems atrophy), Arai et al. suggest that p62 is involved in the formation of inclusions in these disorders. Because p62 is present in other abnormal protein deposits, however, it is not likely to be the major protein component in the ubiquitinated inclusions of FTLD-MND and FTLD-MND-type.

Mizuno et al.[39] showed that valosin-containing protein (VCP, which they propose calling 'vacuole creating protein'), labels inclusions of FTLD-MND. VCP is a member of the ATPase family and a putative sensor protein for degenerating proteins, and is the same as polyglutamine-interacting protein 1, previously reported to label Lewy bodies and the polyglutamine inclusions in Huntington disease and Machado-Joseph disease. In their paper, Mizuno et al. also showed that VCP labels Lewy bodies, Lewy neurites, dystrophic neurites of plaques in Alzheimer disease, ballooned neurons, and Marinesco bodies, but not granulovacuolar degeneration or NFTs, and therefore VCP is also not likely to be the major protein component in the ubiquitinated inclusions of FTLD-MND and FTLD-MND-type. VCP is also present in the ubiquitinated inclusions of inclusion body myopathy associated with Paget's disease of bone and FTD (IBMPFD).[40,41]

ALS AND OTHER CAUSES OF DEMENTIA

DLDH

Surprisingly, the one case of DLDH remaining in our NP core after re-classification is an ALS case. This subject displayed signs of disinhibition and poor judgment. General gross and histologic findings were compatible with a frontotemporal lobar dementia. Despite repeating the ubiquitin immunostains at higher concentrations, no ubiquitinated inclusions could be identified, and we had to conclude that the pathologic diagnosis was most consistent with DLDH. Tau and neurofilament immunostains were also negative.

Alzheimer disease

Recently, Hamilton and Bowser[42] described seven cases of ALS with dementia. Four of these had pathologic FTLD-MND and two had Alzheimer disease (AD) pathology. These two cases were both CERAD C, but Braak stages were IV and II in the two cases. Therefore, by NIA/Reagan criteria, neither of them would be classified as 'high likelihood dementia due to AD'.

In our 76 cases of ALS (mean age 60), all cases that were demented had the pathology of FTLD-MND, except the one case of DLDH noted above. None of the nondemented cases had sufficient AD pathology for the concomitant diagnosis of AD. The two cases with the most severe AD pathology (ages 63 and 76) had CERAD C, Braak IV, NIA/Reagan 'not classifiable'. Fifteen additional cases have AD pathology consistent with aging (CERAD 0-C, Braak I-II, ages 54–87 with a mean age of 69).

ALS with dementia pugilistica-like neurofibrillary degeneration

In our 76 ALS cases, we have 6 with clusters of tau-, Gallyas-, and thioflavine-S-positive neurofibrillary tangles, many in a perivascular distribution, some with occasional tau-positive astrocytes. These were all males without a history of dementia, and their ages at death were 38, 41, 44, 46, 56, and 69. None had a history of repeated severe head trauma, but most had experienced some form of head trauma or had been involved in activities that would expose them to potential head trauma (see Table 13.2). The most striking example is case 4, a 46-year-old, and the most severely affected region was the temporal lobe, where massive clusters of tangles were present (Fig. 13.8A–D). In this case, only four NFTs were observed in the entorhinal cortex (Fig. 13.9), unlike what would be expected were the cortical pathology that of AD. In case 6, a 69-year-old man, there were moderate NFTs in the entorhinal cortex, and one might argue that the changes were those of AD-aging. While the cortical NFTs were sparse

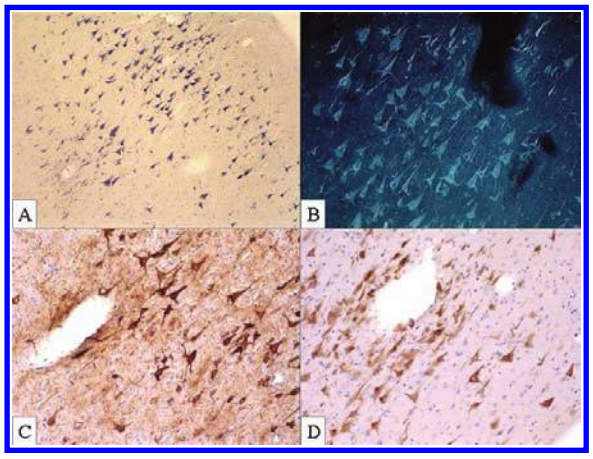


Fig. 13.8 ALS case, nondemented, 46 years old. Superior temporal gyrus neurofibrillary tangles. (A) Gallyas. (B) Thioflavine-S. (C) AT8. (D) MN423.

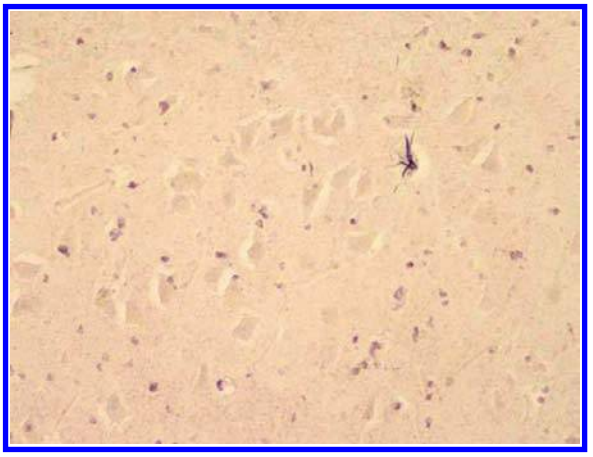


Fig. 13.9 Entorhinal cortex, Gallyas.

Table 13.2 Potential head trauma

Case no.	*Age (years)*	*Activity with potential head trauma*
1	38	Epilepsy from age 3–6 years attributed to a difficult delivery; major altercation with wife, hit hard enough on the back of the head to require hospital admission – skull fracture, LOC unknown
2	41	Avid cyclist, accident in 1989 resulted in clavicle fracture
3	44	No head trauma that caused LOC, but brick fell on his head, early 30s
4	46	Banged head repeatedly on crib as infant; history of facial tics as teenager, high school wrestler for about a year (no injuries recalled); 10 years before onset of ALS had 'raccoon eyes' and mentioned altercation but gave no details
5	56	High school wrestler, no injuries recalled; few months before ALS onset had MVA where head broke windshield, no LOC
6	69	In an MVA without LOC; history of playing football, but no recalled injuries

LOC, loss of consciousness; MVA, motor vehicle accident.

in this case, they were present in clusters in the motor cortex, and there were large numbers of tau-positive astrocytes in the midline white matter of the medulla and in one ventral CST in the cervical spinal cord. We do not know the significance of the DP-like neurofibrillary degeneration in these cases, and before making any conclusions, we need to know whether the other cases in our ALS files had a history of activities with potential for head trauma. However, dementia pugilistica-like pathology such as that present in our cases has previously been reported in young men with mild chronic head injury.[43]

CONCLUSIONS

Most cases of ALS with dementia have FTLD-MND, the diagnosis of which is made when ubiquitinated inclusions are found in superficial cortex and/or dentate gyrus. FTLD-MND-type appears to be the most common pathologic FTLD subtype. While some familial cases have been linked to chromosomes 17 and 9, no mutations have to date been identified in FTLD-MND or FTLD-MND-type. The major protein component of the inclusions has not been identified as yet.

There is increasing evidence that neurodegenerative disorders share a common process of protein accumulation or deposition due to abnormal production, abnormal processing such as alterations in three-dimensional structure, or altered degradation. Results of studies of FTLD-MND and FTLD-MND-type may shed light on the more fundamental issue, one that may be shared by all neurodegenerative disorders, of potential mechanisms of abnormal protein deposition, regardless of whether these are primary or secondary events, which may ultimately lead to potential novel therapeutic targets.

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14

Amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam

Daniel P Perl

INTRODUCTION

Guam is the largest island in the western Pacific, located approximately 3800 miles west of Honolulu, Hawaii, 1500 miles south of Tokyo, Japan and 1500 miles east of Manila, the Philippines. The island is the largest of 15 islands comprising the Marianas archipelago, measuring 212 square miles in area (about 20 miles long by 4–9 miles wide). Guam is inhabited by approximately 150 000 people, of whom 57 000 are an indigenous native population, referred to as Chamorros. The Chamorros of Guam suffer inordinately from a unique spectrum of central nervous system neurodegenerative disorders which have been the subject of intensive scientific study over the past 40+ years. The condition is referred to locally as 'lytico-bodig' and is more widely known in the scientific literature as amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS/PDC) of Guam.

Patients suffering from various forms of lytico-bodig show in varying degrees the features of the three major age-related neurodegenerative disorders seen elsewhere in the world, namely Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS). Guam has been regarded as a unique location where etiopathogenic concepts may be explored among the affected population. It is felt that a better understanding of ALS/PDC will not only provide valuable insights into these specific disorders, as seen in the Chamorro population, but also provide a means for addressing such concepts in the comparable neurodegenerative disorders encountered throughout the world. A number of earlier chapters have discussed these concepts, in general. Here we will discuss the disorders of the Chamorro of Guam within the context of frontotemporal degenerations and their association with dementia and motor neuron disease. As we believe that Guam ALS/PDC can provide important insights about many aspects of Alzheimer's disease, Parkinson's disease and ALS, as it is seen elsewhere in the world, we similarly believe there are relevant lessons from a perspective of the Guam disorder for those who struggle to understand the frontotemporal degenerations and their association with dementia and motor neuron degeneration.

ALS/PDC OF GUAM

ALS of Guam

As part of the final phases of the Pacific campaign of World War II, Dr Harry Zimmerman, a pathologist with an interest in nervous system disease, was a medical officer stationed by the US Navy on Guam. In June, 1945, he wrote to his superiors in the Navy that he had observed an apparent high prevalence of ALS among the native population on the island.[1] He specifically noted that he had encountered seven or eight patients with clinically apparent ALS on the medical wards of the small civilian hospital of Guam. In the month of May, 1945 he had personally confirmed the diagnosis at autopsy in two of these patients. Faced with this apparently high prevalence of what is a relatively uncommon disease among a rather small native population, Zimmerman suggested a possible genetic etiology for the problem and recommended that further investigation be undertaken following the conclusion of the war.

Indeed, the studies Zimmerman recommended were carried out in the 1950s by Koerner[2] and Arnold et al.[3] and were then taken over by Mulder and Kurland.[4,5] These studies clinically characterized ALS among the native Chamorro population as being virtually identical clinically to the disease as it is seen elsewhere in the world. Clinical features include insidious onset with weakness, clumsiness and/or unexplained weight loss. Clinical signs in the early phases of the disease include muscular atrophy, prominent fasciculations and hyperreflexia. The condition progresses inexorably with prominent muscular atrophy, profound weakness and areflexia prior to death. The typical length of survival is 2–4 years from clinical onset, although in about 10% of cases a slower progression with more prolonged survival is seen.[6] Prevalence rates for ALS on the island of Guam were calculated to be over 100 times that previously documented in any other population.[7,8] Indeed, prevalence rates for some of the smaller native villages on the southern part of the island were said to be over 1000 times greater than those seen elsewhere in the world.

The neuropathologic features of ALS of Guam were initially characterized in the seminal publications of Asao Hirano, a neuropathologist/neurologist who began his distinguished career with a stay of several months on Guam, where he examined affected natives and performed autopsies on those who had died.[9,10] Hirano described the brains of affected patients as being characterized grossly by a modest degree of cerebral cortical atrophy which, although it predominates in the frontal and temporal lobes, does not show the distinct sparing of parietal and occipital lobes seen in cases of Pick's disease or other forms of frontotemporal dementia (FTD). Although not typical, in some Guam cases severely affected by ALS, grossly visible atrophy of the primary motor cortex may be observed. However, inspection of the spinal cord nerve roots usually reveals prominent atrophy of the ventral motor roots.

Microscopically, there is prominent loss of both upper and lower motor neurons. In addition, in the primary motor cortex and the anterior horns, shrunken pyknotic remaining neurons are also observed. Loss of myelin in the descending corticospinal tracts is typically prominent and may often be well seen in both the lateral (crossed) and anterior (uncrossed) pathways. Ubiquitinated intraneuronal inclusions may be demonstrated in affected areas by immunohistochemistry, although in end-stage cases there may be such severe neuronal loss of anterior horn cells that this is difficult to document. In about 10% of cases small eosinophilic Bunina bodies may be seen in remaining anterior horn cells. There are usually relatively small numbers of such bodies but in some cases they may be numerous.

In 1961, Nathan Malamud in collaboration with Hirano and Kurland made the observation of the presence of widespread severe neurofibrillary tangle (NFT) formation in the ALS cases of Guam.[9] Indeed, virtually every case had such changes. NFTs were observed in the hippocampus (Fig. 14.1), entorhinal cortex and neocortex, in general. The involvement of the neocortex by NFTs predominates in more superficial layers (primarily layers II and III) as opposed to deeper layers (layer V and superficial VI)[11] (Fig. 14.2). This pattern of involvement is the reverse of what is seen in cases of Alzheimer's disease. Involvement by NFTs may also be seen in the primary motor cortex as well as in anterior horn cells of the spinal cord.

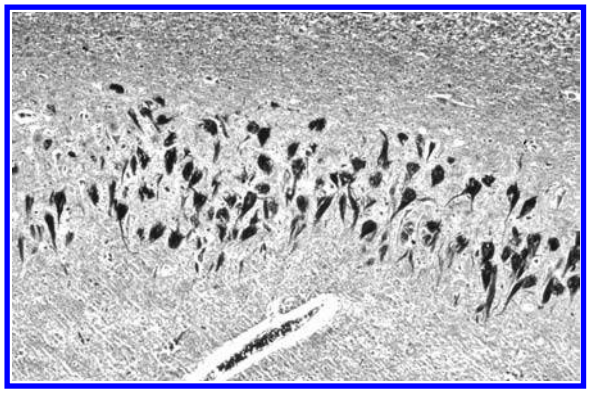

Fig. 14.1 CA1 region of hippocampus of Guam ALS cases showing prominent NFT formation. Modified Bielschowsky stain.

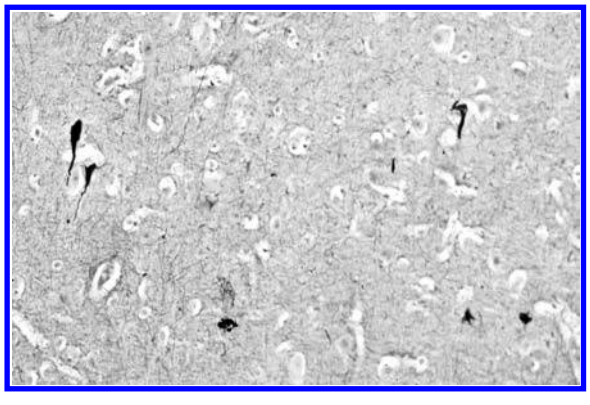

Fig. 14.2 Neocortical NFTs of Guam ALS cases. Modified Bielschowsky stain (inferior frontal cortex).

The involvement by NFTs in the neurons of the CA1 region of the hippocampus can be quite severe and in such cases, prominent neuronal dropout with extracellular 'ghost tangles' is seen. It is noteworthy that despite such extensive neocortical and hippocampal involvement by NFTs, such patients have appeared to retain intact cognitive function even into the late stages of the disease. However, it should be noted that end-stage ALS patients typically have difficulty communicating, with dysphonia or aphonia related to preterminal extreme weakness or paralysis of the muscles of respiration and vocalization. Nevertheless, within their physical limitations, Guam ALS cases appear to be able to follow verbal commands and to be aware of their surroundings. This would suggest that severe involvement by NFTs in such regions (especially the hippocampus) may not necessarily be associated with profound cognitive impairment, in contradistinction to what most students of the neuropathology of dementia in other settings would declare.

The NFTs encountered in Guam ALS cases are virtually identical to those of Alzheimer's disease. They are immunoreactive to abnormally phosphorylated tau[12] and show a paired-helical fiber appearance on electron microscopic examination.[13] Biochemical studies[14] have shown the accumulation of the three-repeat form of tau, as is seen in cases of Alzheimer's disease. Importantly, despite the presence of large numbers of NFTs, virtually identical to those of Alzheimer's disease, the Guam cases were free of senile plaques or vascular amyloid deposition. As such, Guam ALS may rightfully be considered an example of a *tauopathy*. The presence of NFTs in the brains of Guamanian Chamorro patients with ALS clearly differentiates these specimens from those of sporadic cases of ALS seen elsewhere in the world.[15]

PDC of Guam

In carrying out the initial door-to-door clinical survey studies of ALS on Guam, a significant number of other natives were identified to be suffering from a different neurologic disorder that displayed a picture of prominent parkinsonian features in association with dementia. In 1961, this disorder was first described, both clinically and neuropathologically, in two classic articles by Hirano, where the condition was named parkinsonism-dementia complex (PDC) of Guam.[16,17] PDC of Guam is characterized clinically by muscular rigidity, bradykinesia and gait disturbance. Although a 4–7 Hz pill-rolling resting tremor may be seen in some patients, it is not a prominent clinical feature. As the disease progresses, increasing rigidity and bradykinesia become particularly disabling. These parkinsonian features do not show a sustained clinical response to levodopa.[18]

Accompanying the parkinsonian features is a profound progressive dementia. The cognitive losses include recent memory impairment, disorientation and difficulty with reasoning and

ability to perform simple calculations. The neuropsychological profile of PDC cases is indicative of a global dementia with a broad impairment of virtually all areas of cognitive function, including orientation, recall, language, visuospatial and constructional tests and frontal executive tasks.[19] In this regard, Guam PDC cases more closely follow a pattern similar to that seen in Alzheimer's disease, as opposed to that of FTDs or the subcortical dementias. PDC cases may initially present with dementia and then subsequently show parkinsonian features, may present with parkinsonism with intact cognition with subsequent development of dementia, or may present with both major features simultaneously. Nevertheless, all these forms of presentation progress rapidly with a typical total survival time from diagnosis to death of 5–6 years.

The neuropathologic features include rather prominent cerebral cortical atrophy. Similar to the ALS cases, although the cerebral atrophy predominates in the frontal and temporal lobes, it is not lobar in nature and complete sparing of the parietal and occipital lobes is not encountered. Upon dissection, the substantia nigra and locus coeruleus are notably depigmented on gross inspection. The lateral ventricles of advanced cases may be dramatically enlarged, especially in the temporal horns (Fig. 14.3).

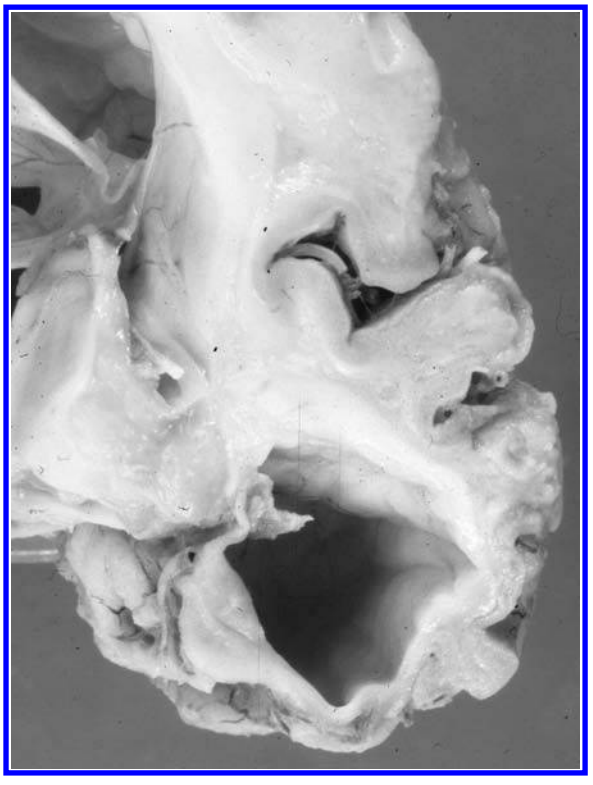

Fig. 14.3 Appearance of coronal section of temporal lobe showing prominent atrophy with dramatic dilation of the temporal pole of the lateral ventricle in a case of Guam PDC.

Microscopically, there is dramatic loss of pigmented neurons of the substantia nigra pars compacta and locus coeruleus. The few remaining neuromelanin-containing neurons in these sites typically contain NFTs. Since such cells are rounded in contour, as opposed to the typical pyramidal-shaped neurons of the neocortex or hippocampus, such NFTs appear as intertwining rounded fibrils and are referred to as globoid tangles (Fig. 14.4). In only about 10% of PDC cases are Lewy bodies identified in remaining neurons of the substantia nigra (Fig. 14.5) and the locus coeruleus. When present the Lewy bodies are encountered in only very small numbers.

PDC cases also show severe and widespread involvement by NFTs with severe involvement of the CA1 and subicular regions of the hippocampus, entorhinal cortex, basal nucleus of Meynert and neocortex (Fig. 14.6), in general.

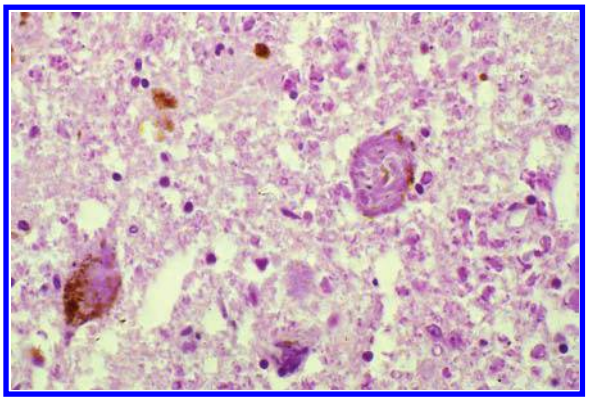

Fig. 14.4 Globoid NFT of pigmented neuron of the substantia nigra pars compacta in a case of Guam PDC. Hematoxylin and eosin stain.

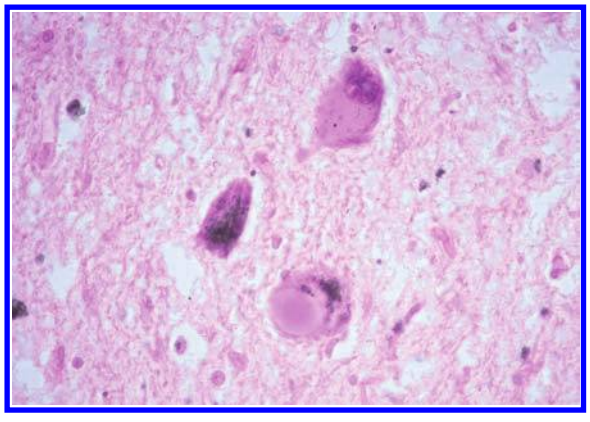

Fig. 14.5 Rare Lewy body in pigmented neuron of the substantia nigra pars compacta in a case of Guam PDC. Hematoxylin and eosin stain.

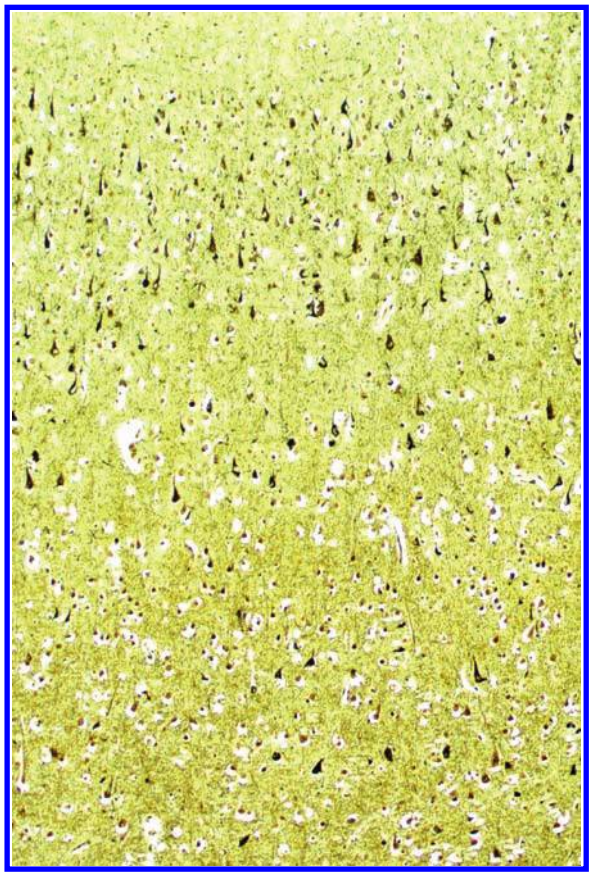

Fig. 14.6 Prominent neocortical NFTs in a case of Guam PDC. Modified Bielschowsky stain.

Involvement of other brainstem nuclei and the dentate nucleus of the cerebellum (Fig. 14.7) is also encountered. Once again, despite the widespread NFT formation and the presence of dementia in the PDC patients, Hirano noted that there was surprisingly little vascular amyloid deposit or senile plaque formation. It is of interest that senile plaque formation is now being noted in some of the more recently autopsied cases. It appears that the neuropathologic substrate of Guam PDC has changed in the past 30–40 years, suggesting that altered environmental factors have played a role in such alterations.

ALS and PDC of Guam: separate disease entities or a single form of neurodegeneration with a wide spectrum of clinical and neuropathologic features?

As noted above, ALS of Guam and PDC were initially described separately and in most clinical and epidemiologically based studies have been considered to be two distinct clinical and neuropathologic entities which occur in high incidence and prevalence in the same population. Despite this, with further investigation a considerable amount of evidence has accumulated suggesting that in both clinical manifestations and, in particular, neuropathologic features, there are numerous examples of

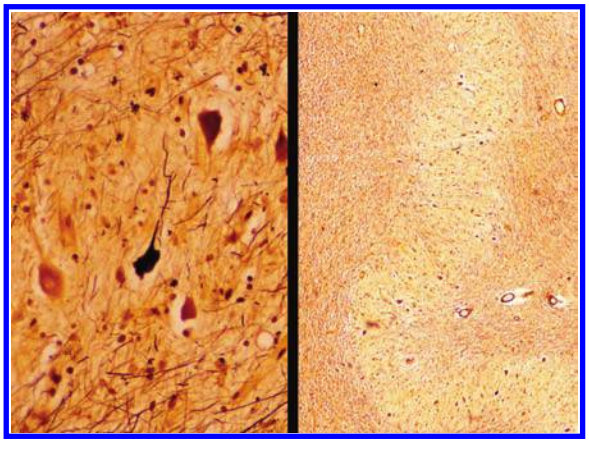

Fig. 14.7 NFTs in neurons of the dentate nucleus of a Guam PDC case. Low- and high-power photomicrograph, modified Bielschowsky stain.

overlap between the two conditions. This evidence suggests that, at the very least, they share pathogenic mechanisms and may even represent a single entity with a wide spectrum of neurodegenerative involvement.

It is rare that cases of ALS of Guam show clinical evidence of parkinsonian features. In a clinical study, Elizan and colleagues[20] reported that only 5 of 104 diagnosed cases of ALS on Guam progressed to develop a definite picture of PDC in subsequent clinical examinations. However, they did note that in an additional five cases clear parkinsonian signs were identified but these were seen in the absence of evidence of cognitive decline. Rogers-Johnson and coworkers,[21] in a retrospective review of clinical data, reported that in patients diagnosed with ALS minimal parkinsonian features were identified in only 5% of cases and dementia was identified in 4% of cases. Nevertheless, ^{18}F-6-fluorodopa PET studies of four Guam ALS cases, said to be free of clinical evidence of parkinsonism, showed clear-cut evidence of decreased striatal fluorodopa uptake.[22] The degree of fluorodopa uptake loss was intermediate between that seen in clinically diagnosed PDC cases and normal controls but, at the very least, this was indicative of some extent of substantia nigra pars compacta neuronal degeneration in what clinically appeared to be 'pure' Guam ALS cases. While this study involved only a small number of patients, it does suggest that Guam ALS cases can harbor a significant degree of neurodegeneration of nigrostriatal dopaminergic input to the striatum yet be clinically free of the signs and symptoms of parkinsonism.

Neuropathologic studies of Guam ALS cases have shown a somewhat different story. In studies of the distribution of NFTs in cases of Guam ALS, in virtually all cases Hirano demonstrated clear evidence of tangles in the substantia nigra, locus coeruleus and other brainstem nuclei.[15,23] Rogers-Johnson et al.[21] reviewed the neuropathologic features of 209 Guam ALS autopsies over a 30-year period and reported evidence of depigmentation and neuronal loss in the substantia nigra in 63% of these cases. These data raise the question of why there is so little clinical evidence of extrapyramidal dysfunction in Guam ALS cases, despite the presence of a significant degree of substantia nigral pathology? A possible explanation is that in patients with ALS the skeletal musculature has undergone extensive denervation and in the presence of ongoing pathology of upper and lower motor units (as well as denervation atrophy of the skeletal musculature) the loss of the integrity of the nigrostriatal pathways may be clinically masked. Despite the lack of clinical supporting evidence, the neuropathologic data reveal that in the majority of Guam ALS cases the neurons of the substantia nigra pars compacta are also affected by the neurodegenerative process.

In comparison, if one looks at motor system involvement in PDC cases, superimposed clinical evidence of amyotrophy is rather commonly observed. In a longitudinal clinical study, Elizan and colleagues[20] examined this question and reported that 38% of PDC cases subsequently progressed to develop clinical manifestations of ALS. In addition, electromyographic studies of 12 'pure' PDC cases revealed electrical evidence that were considered diagnostic of lower motor neuron damage.[20] It should be noted that a more recent neurophysiologic study[24] failed to document this degree of overlap. The retrospective clinical review by Rogers-Johnson et al. showed that of patients with PDC, 34% were noted to have developed a positive Babinski sign and 32% showed fasciculations and/or muscular atrophy on clinical exam, all indicative of upper and/or lower motor neuron involvement.[21]

Neuropathologic studies of PDC cases also show extensive evidence of overlap with ALS. For example, in Hirano's initial description of PDC,[17] he noted neuropathologic evidence of typical morphologic changes of ALS in the spinal cords of 17 of 48 cases (38%). In a review of 113 autopsies of PDC cases on which spinal cord examination had been performed,[21] 35% showed evidence of lateral corticospinal tract demyelination as well as anterior horn cell loss.

In looking at the above evidence, it is clear that relatively few truly 'pure' cases of either ALS or PDC are actually encountered on Guam. Indeed, it could be argued that the approaches taken to investigate overlap, both clinically and especially morphologically, were not designed to detect

more subtle evidence of simultaneous involvement. Had more refined and, in particular, quantitative morphologic measures been used, greater evidence of overlapping features would probably have been found. This has suggested to us that, especially from the perspective of the neuropathologist, the pattern of clinical features leading to the clinical diagnosis of Guam cases reflects the effects of a rather widespread progressive neurodegenerative process that typically involves the motor system, basal ganglia, hippocampus and neocortex in varying degrees. The particular brain region that initially becomes significantly affected by the neurodegenerative process will determine the initial clinical manifestations and define the clinical diagnosis that is made. As each case progresses to involve additional brain regions, other clinical manifestations will become evident. Eventually, the clinical distinctions which define these separate disorders will become more difficult to delineate since the pattern and extent of neuropathologic involvement has become so widespread and severe. These observations have suggested the possibility that a unifying neurodegenerative process and therefore a single disorder underlies Guam ALS/PDC but with varying extents of neuropathologic involvement, leading to the clinical variants that are encountered among patients that are diagnosed. We believe that this concept has important implications for nosologic designations of the analogous age-related disorder seen elsewhere in the world and certainly needs to be considered in the context of varying forms of frontotemporal neurodegenerative disorders and their association with dementia and motor neuron dysfunction.

DO PROTEIN AGGREGATES DEFINE THE VARIOUS NEURODEGENERATIVE DISORDERS?

Recently, it has become fashionable to define the various neurodegenerative diseases by identifying the major protein that aggregates within affected cells. This has led to subclassifying disorders as being tauopathies and synucleinopathies, etc. In accordance with this concept, Guam ALS/PDC, with its severe and widespread involvement by NFTs, has been considered to represent a prime example of a tauopathy. Indeed, severely involved cases of Guam PDC probably have more brain accumulation of tau than any other disorder to which man is subject. The intraneuronal tangles are heavily ubiquinated and anti-ubiquitin immunostains dramatically display the extent of involvement.

However, as has been demonstrated recently by Yamakazi et al.[25] and by Forman and coworkers,[26] approximately 60% of ALS/PDC cases show evidence of varying degrees of intracytoplasmic intraneuronal α-synuclein immunoreactive Lewy body-like inclusion bodies in the amygdala (Fig. 14.8). α-Synuclein immunoreactive spherical bodies have also been demonstrated in the molecular layer of the cerebellar cortex in 63.6% of cases of Guam PDC.[27] The aggregates of α-synuclein in both the amygdala and cerebellum are prominently ubiquitinated. Although Guam ALS/PDC cases infrequently show evidence of Lewy bodies in the substantia nigra and typically do not display cortical Lewy bodies, these findings indicate that a majority of cases also undergo α-synuclein aggregation in the course of their disease, again suggesting an overlap with the synucleinopathies. Similar findings have been noted in cases of Alzheimer's disease, both in sporadic and familial settings,[28,29] as well as in cases of Parkinson's disease.[30] The simultaneous observation of both tau and α-synuclein aggregation indicates that

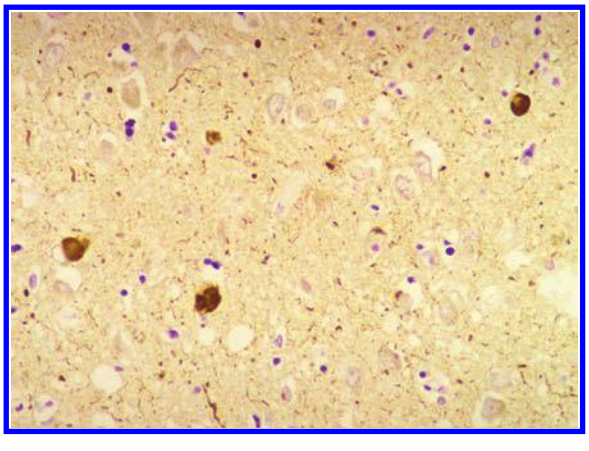

Fig. 14.8 Prominent intraneuronal inclusion body formation in amygdala of Guam PDC case. Anti-α-synuclein immunohistochemical preparation.

protein aggregation is a general feature of the process of neurodegeneration. Whether such protein aggregation induces neuronal dysfunction and death, is a result of neuronal damage from other causes, or even represents an attempt at repair from damage, remains unclear.

ETIOLOGIC CONCEPTS

From its very first identification, interest in the phenomenon of Guam ALS/PDC has centered on the identification of the underlying etiology of this high incidence focus occurring in such a remote island community. Zimmerman, with his initial observation of large numbers of ALS cases in the Chamorro population, suggested that this was due to an inherited disorder in an isolated, inbred community.[1] Over the years, it has become clear that there are certain families living on Guam that have a very high percentage of offspring affected by the disease, while other families have been relatively spared.[31,32] Due to the very high prevalence of ALS/DPC on Guam, especially in earlier decades, virtually no Chamorro family on the island has been left completely free of the disease. Although there are likely to be genetically based susceptibility factors in play, as will be discussed below, it has become clear that the concept of Guam ALS/PDC having an hereditary etiology is incorrect and that the primary cause lies in exposure to putative environmental factor(s) present on Guam. Studies on Guam to identify an underlying genetically based locus have been largely disappointing.[33,34]

Epidemiologic findings have supported the concept that environmental factors are primary in the etiology of Guam ALS/PDC. Initial studies performed in the 1960s and 1970s demonstrated that ALS was the predominant form of neurodegeneration among Chamorros, although many cases of PDC were also present. Over the ensuing decades the numbers of Chamorros with ALS have steadily dropped while PDC still remains relatively common on the island.[19,35,36] Today it is rather rare to encounter new cases of ALS on Guam, although these are occasionally seen and, when subjected to autopsy, prominent NFT formation consistent with the Guamanian form of the disease is typically encountered. In addition, the age of onset has significantly changed over the past 30 years. In the interval of 1955–1965, the mean age of onset of ALS among Chamorros was 47 years and that of PDC was about 52 years. This compares with the mean age of onset for cases diagnosed between 1985 and 1995 of ALS cases at 53 years of age while PDC cases began at 64 years.[19,36,37] This kind of drastic change in a relatively stable population of the basic distribution and characteristics of a disease – all within the interval of less than one generation – does not occur in inherited disorders, which tend to remain rather constant over years of observation. Rather, such dramatic changes reflect the changing impact of relevant environmental etiologic factors or, at the very least, changes in potent modifying environmental factors.

It should be pointed out that since the end of World War II, drastic changes have taken place in many aspects of life on Guam. For example, in the immediate, post-World War II period the island's population had an entirely self-sufficient food supply and what might be considered a western lifestyle was virtually absent among the Chamorro population. Based on a number of political, cultural and economic influences, by the end of the twentieth century Guam has become completely westernized and all aspects of modern western 'culture' (fast food restaurants, golf courses, satellite TVs, pick-up trucks, etc.) are now part of the way of life of Chamorros on the island. Foodstuffs on the island are imported and dietary intake on Guam is now virtually entirely derived from off-island sources.

It should also be pointed out that preserved death certificate records on Guam dating from the early 1900s document the presence of numerous deaths from ALS among the native population. This clearly suggests that the putative environmental etiologic agent was present on the island long before this process of westernization took place. It would appear that the introduction of modernization and the importation to Guam of many new and potentially etiologic factors in the post World War II era cannot be considered to be the cause of Guam ALS/PDC. This modernization can

only have modified the way in which people living on Guam are exposed to the putative on-island etiologic factor or possibly has modified the population's response to that underlying exposure.

An important observation pointing towards an environmental etiology for Guam neurodegeneration has been the appearance of cases of ALS and PDC among Filipino migrants to Guam with long-term residence on the island. Beginning in the immediate post-World War II era and extending to the present time there has been a significant migration of individuals born and raised in the Philippines who now live permanently on Guam. The Filipino migrant community on Guam currently numbers approximately 40 000 individuals, mostly males who have come in search of stable employment. Many are relatively recent arrivals but a good number have resided on Guam for over two decades. Within the Filipino community living on Guam for an extended period, a considerable number of cases of ALS have now been documented. These cases were first noted by Reed and Brody in 1975[7] and subsequently, Garruto and co-workers[38] documented nine additional Filipino migrant cases of ALS and two cases with apparent PDC. Virtually all of the cases were of Filipino men who moved to Guam in the late 1940s and early 1950s. A small number of autopsies have been performed on ALS cases among the Filipino migrants and NFTs were documented in the brain specimens in about 50% of cases. The extent of NFT involvement was not as dramatically widespread as is typically encountered in the native Chamorro cases, but this finding clearly separates them from sporadic cases of ALS,[15,23] as seen elsewhere in the world since NFTs are not a prominent neuropathologic feature of ALS, especially among these relatively young patients.

Importantly, the appearance of cases of PDC among the Filipino migrant population further reinforces the concept that long-term residence on the island underlies the cause of the outbreak of neurodegenerative disease. ALS is a disorder that has been seen throughout the world, yet PDC remains confined solely to the island of Guam and the Kii peninsula of Japan.[39] Three of these Filipino migrant cases have been confirmed by autopsy.[40,41] These autopsy-proven cases represent important evidence that ALS/PDC is not a disorder that is confined to the native Chamorro population living on Guam, but may also be seen in Filipinos who have migrated to the island and have lived in this environment for many years. Unless there is a hitherto unrecognized focus of ALS/PDC in the Philippine islands, then these findings strongly support the concept that long-term exposure to a putative environmental agent on Guam is responsible for the epidemic.

The nature of the specific underlying environmental factor(s) on Guam has been under consideration over many decades and is well discussed in several prior publications.[42–44] Briefly, these considerations have centered on investigating three competing hypotheses, namely, the long-term effects of neurotropic infectious agents, potentially neurotoxic components of the seed of the false sago palm, *Cycad circinalis*, and the possible neurotoxic effects of trace element abnormalities leading to prominent aluminum deposition in the brains of ALS/PDC victims. Each will briefly be discussed.

Infectious agents

The initial identification of PDC, with its prominent parkinsonian features, led some to give serious consideration that the nature of the outbreak of neurodegenerative disease on Guam might be post-infectious in nature. Similarities of PDC to post-encephalitic parkinsonism patients who had survived the epidemic of encephalitis lethargica in the early part of the twentieth century were noted. Post-encephalitic parkinsonism typically displays a period of latency between the initial episode of encephalitis and the onset of parkinsonian symptoms. That latency period may last as long as a decade or more; however, 6 months to a year was more typical.[45] Neuropathologic features of post-encephalitic parkinsonism include many of those encountered in the PDC of Guam, especially the presence of globoid NFTs in the remaining neurons of the substantia nigra, in the absence of nigral Lewy bodies, and the finding of neocortical NFTs predominating in superficial layers (layer II/III).[46]

Assays of both serum and post-mortem brain tissues of ALS/PDC victims have failed to show any consistent evidence of a preceding central nervous system infection.[47] Archival death certificates dating from the beginning of the twentieth century fail to document any major outbreaks of encephalitis in the community and interviews with knowledgeable elders on Guam failed to provide anecdotal accounts of any notable episodes of encephalitis on the island. Relatively restricted outbreaks of Japanese B encephalitis and mumps did occur on Guam in December, 1947 and April, 1948 but subsequent interviews of ALS/PDC patients and their families has failed to confirm a prior history of encephalitis in these cases.

Gibbs and Gajdusek[48] also considered the possibility that Guam ALS/PDC represented a prion-related disorder. These workers made numerous attempts to transmit disease through the intracerebral inoculation of Guam-derived brain tissues into nonhuman primates and other susceptible species. All such attempts have been negative, as were other efforts to recover a transmissible agent through inoculation of tissue culture. In the face of this extensive negative evidence it is difficult to consider that there is sufficient evidence to continue to pursue a possible infectious etiology for ALS/PDC.

Cycad contents

Over the years, an important candidate for the etiology of ALS/PDC of Guam has been the ingestion of putative neurotoxins present within the seed of the false sago palm, *Cycas circinalis*. This form of cycad tree is an indigenous plant on Guam and its seeds have traditionally served as a food source for Chamorros. However, the raw seeds contain a potent and potentially fatal hepatotoxin and require extensive washing in water before they may be safely eaten. The natives wash the seeds for a week or more, prepare flour by grinding the dried seed and on occasion use this to make tortillas, porridge and doughnuts and to thicken soups. In 1964, Marjorie Whiting proposed that a neurotoxin might be present in the seeds and might be responsible for the onset of neurodegenerative disease.[49] This suggestion gave rise to a series of detailed toxicologic studies of cycad and its constituents. The results of these studies were reported in six Cycad Conferences held under the auspices of the National Institutes of Health.[50–52]

An important outcome of this toxicologic research was the identification of cycasin (methylmethoxymethanol β-D-glucosidase), a potent alkylating agent present within the cycad seed. Cycasin represents one of the most potent known naturally occurring carcinogens and many of the cycad-exposed animals developed cancers involving their lungs, kidneys, and liver. Importantly, despite the high doses being used and the wide range of animals that were exposed, little, if any, evidence of actual neurotoxicity was demonstrated in these experiments. Based on this entirely negative evidence, support for the cycad hypothesis as the etiology of the Guam outbreak of neurodegeneration waned for several decades.

However, in 1987, Spencer and colleagues[53] reported the experimental induction of a parkinsonian state accompanied by motor weakness in cynomologus monkeys fed large oral doses of an 'unusual' amino acid present in small amounts in the cycad seed, namely β-N-methyl-amino-L-alanine (BMAA). Each monkey was fed orally for up to 13 weeks with a large daily dose of BMAA. The BMAA employed had been synthesized chemically and was not derived from the natural source. The animals were reported to show muscular weakness, masked facies and a loss of aggressiveness, and the authors suggested that these features had a similarity to ALS/PDC in man. Based on this observation the authors suggested that BMAA could represent the etiologic agent responsible for the neurodegenerative condition on Guam.

However, these conclusions have been questioned on a number of grounds. The monkeys received BMAA doses that were extraordinarily high (100–300 mg BMAA/kg body weight/day), especially since Duncan et al.[54,55] reported that BMAA is present in very small concentrations in raw cycad seed (0.1% or less, by weight) and is readily removed by even brief washing. Duncan et al. estimated that an

adult human would have to ingest approximately 7 kg of unwashed raw seed per day to receive a dose that was comparable to that given to the exposed animals. Since raw cycad seed is highly toxic to humans and must be washed repeatedly before it may be safely eaten, most of the BMAA would have been removed. Accordingly, a comparable dose of washed cycad seed would require ingestion of approximately 70 kg of cycad flour per day. Additional studies questioned whether BMAA was even capable of crossing the blood–brain barrier.[56,57] Importantly, neither a striatal dopaminergic deficit (indicative of nigral degeneration) or denervation atrophy (suggesting anterior horn cell pathology) were documented in the exposed monkeys and it remains unclear why these monkeys displayed any of their neurologic signs. Spencer and colleagues[58] have subsequently admitted that 'the changes [induced in monkeys fed synthetic BMAA] fall short of a model of the human disease.'

Most recently, Cox and colleagues[59] have overlooked these concerns about BMAA as a possible neurotoxin and have nevertheless hypothesized that the local custom among some Guam natives of consuming fruit bats could serve as a source of biomagnified BMAA for victims of ALS/PDC. In support of this concept, they report finding evidence of increased concentrations of BMAA in cyanobacteria, cycads, skin tissues from preserved museum specimens of fruit bats and human brain tissues.[60,61] We have subjected brain tissues derived from Guam PDC cases and a variety of control tissues to detailed analysis and found no detectable levels of BMAA in any of our samples.[62]

Finally, Shaw and colleagues[63–66] have reported evidence that washed cycad seed contains neurotoxic properties that can be demonstrated both *in vitro* and in mouse-feeding experiments. They have proposed the presence of sterol glycosides as the putative neurotoxic factor in such preparations. Using oral feeding of washed cycad they have reported evidence of motor and behavioral dysfunction in mice accompanied by evidence of apoptosis and neuronal loss in selected brain regions. The relevance of these experimental findings to the human disorder remains unclear.

Toxic metals

In 1972, Yase[67] first suggested the possibility that the neurodegeneration seen on Guam might be related to an abnormal accumulation of potentially neurotoxic metals. He noted that manganese and aluminum, metals associated with neurotoxic properties, were present in significant amounts in the soils of Guam. In 1980, using the techniques of electron probe microanalysis, we first demonstrated evidence of aluminum accumulation in the NFT-bearing neurons of cases of Alzheimer's disease.[68] Subsequently, using a similar approach, Perl and colleagues[69] showed evidence of dramatic aluminum accumulation in the tangle-bearing neurons of patients with ALS/PDC of Guam. Additional studies indicated that the concentration of aluminum in the tangle-bearing neurons of the Guam cases was approximately 10 times greater than that of Alzheimer's disease cases.[70] Although the association of aluminum and Alzheimer's disease remains controversial, the finding of excess aluminum in the tangles encountered in Guam ALS/PDC cases has now been confirmed in a number of different laboratories using five different physical methods.[71–74]

However, despite the reproducibility of this finding, the environmental source of these dramatic intraneuronal accumulations of aluminum or their significance remains unclear. One hypothesis for the observation has been that a deficiency on Guam of environmental sources of calcium and magnesium, both physiologically essential ionic constituents, could result in an increased uptake of aluminum, a potential alternative dietary source of cations.[75] However, studies looking for evidence of a dietary calcium deficiency among Guamanians have been negative[76,77] and other explanations for the excess brain aluminum concentrations must be sought.

Laser microprobe mass analytic studies[78] have demonstrated that the NFTs of Guam cases contain excess iron, as well as aluminum, a finding that parallels observations in cases of Alzheimer's disease.[79] Iron and aluminum excess has also been detected in the neuromelanin granules and Lewy bodies of cases of

idiopathic Parkinson's disease.[80–82] Iron, through the Fenton reaction, is a powerful pro-oxidant and is capable of catalyzing the production of the highly reactive hydroxyl radical from hydrogen peroxide, a by-product of normal dopamine metabolism. We have suggested[83] that the combination of iron and aluminum may place a neuron in a state of oxidative stress because of aluminum's apparent ability to enhance iron's capacity to induce lipid peroxidation.[84] Whether the striking aluminum and iron accumulations identified in target neurons for neurodegeneration of ALS/PDC cases are truly etiologic in nature remains unknown. The source of these deposits, the mechanism by which they occur and their consequences remain to be elucidated.

GENERAL COMMENTS

It is a mistake to dismiss ALS/PDC of Guam as a unique condition with little to do with the analogous neurodegenerative disorders encountered elsewhere in the world. Rather, Guam should be viewed as a rich laboratory in which to explore the interactions between environmental and genetic factors in the induction of most of the cardinal features of the age-related neurodegenerative disorders. In this classic nature/nurture interaction, the strongest factor on Guam appears to be environmental in nature. This does not preclude the concept that genetic factors influencing relative resistance or susceptibility to the putative environmental agent(s) are not also present, but these hereditary factors do not apparently play an etiologic role. Thorough studies to delineate such hereditary factors have shown remarkably little. Nevertheless, it is important to continue to pursue such studies since positive results may provide valuable clues as to the nature of the environmental agents with which these genetic factors are interacting. It is clear that when the details regarding the environmental/hereditary interactions occurring on Guam become better understood they will have direct relevance to our understanding of the analogous disorders encountered throughout the world. Within this context, such knowledge should provide insights to our thinking about frontotemporal degenerations and their association with ALS and with dementia.

It is important to point out that Guam provides ample evidence that exposure to certain poorly understood environmental factors can play a significant role in inducing neurodegenerative changes in the brains of exposed individuals. As one who has participated in such research, the search for the putative environmental factor(s) present on Guam has been both tantalizing and frustrating. One would think that with all the efforts spent, over these many years, we would be closer than we currently are to unraveling this mystery. In a similar fashion to that in which important hereditary insights can be gained through the study of genetically based high-risk families, a geographic isolate such as Guam provides opportunities where environmentally based aspects may be more easily addressed. Despite extensive research over several decades, the mystery of the etiology of the remarkable concentration of neurodegeneration on the island of Guam remains unsolved. Despite this, Guam still remains the richest potential laboratory in which to unravel those critical environmental factors of importance to an understanding of the disorders seen on Guam and also the analogous disorders encountered throughout the world.

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15

Neuropathology of the Japanese variants of FTD/ALS

Omi Katsuse, Kenji Ikeda, Kuniaki Tsuchiya, Takashi Togo and Dennis W Dickson

INTRODUCTION

Recent studies concerning amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) have revealed that ALS, ALS with dementia (ALS-D), and FTLD with motor neuron disease (MND)-type inclusions but without MND (FTLD-MNI) exhibit clinicopathological similarities, suggesting a common pathogenesis. Moreover, these disorders share ubiquitin-immunopositive structures that are negative for tau and α-synuclein. We here present corticospinal tract degeneration in Japanese cases with FTLD-MNI, suggesting that ALS-D and FTLD-MNI belong to the same spectrum. We also present a review of the neuropathology of these disorders in the USA and Japan, using ubiquitin immunohistochemistry, and compare US and Japanese cases. Ubiquitin-positive structures in the cerebrum were evaluated – particularly in the caudate nucleus and hippocampal dentate fascia. ALS and ALS-D cases tended to have mild ubiquitin pathology in the caudate nucleus and ubiquitin-positive granular neuronal inclusions in the dentate fascia. In contrast, FTLD-MNI cases had severe neuronal and/or neuritic ubiquitin pathology in the caudate nucleus and ubiquitin-positive Pick body-like or crescent-shaped neuronal inclusions in the dentate fascia. Some major differences between the US and Japanese cases were observed in FTLD-MNI. Clinically, approximately half of the cases in the USA, but none of those in Japan, had a family history of neurodegenerative disease. Neuropathologically, two major variants can be distinguished by their ubiquitin pathologies. In one, there are crescent-shaped neuronal inclusions in the dentate fascia and predominant neuritic structures, often with neuronal intranuclear inclusions (NII), in the caudate nucleus; in the other, there are Pick body-like inclusions in the dentate fascia and many neuronal inclusions, but no NII, in the caudate. Although the former is more common in the USA, most Japanese cases are of the latter variant. This is one reason why it is known as the Japanese variant.

ALS-D

Cases of ALS-D have been described in Japan since 1964,[1–4] and this disease has come to be recognized as a clinicopathological entity. Typical clinical symptoms of ALS-D include initial changes in personality, behavior and/or language, followed by muscle wasting and weakness, with fasciculations in the tongue, shoulder girdle, proximal upper limbs and thorax appearing within approximately 12

months of onset.[1–4] Pathologically, ALS-D is characterized by circumscribed atrophy of the frontotemporal cortices and loss of both upper and lower motor neurons. Therefore, ALS-D has the same clinicopathologic features as both FTD and ALS.

FTD

FTD is a clinical syndrome characterized by early and progressive change in personality, behavior and/or language. The concept of FTD derives from Pick's disease. The original clinical and neuropathological criteria for FTD were proposed by the Lund and Manchester Groups in 1994.[5] According to the criteria, FTD is classified into three subgroups: frontal lobe degeneration type, Pick-type with Pick bodies, and motor neuron disease type. ALS-D corresponds to the motor neuron disease type and is recognized as a subgroup of FTD. However, the concepts and terminology of FTD are confusing, since various clinical and pathological terms have been proposed by different research groups.[6–10] In 2000, therefore, an international working group proposed a conceptual framework for future clinical and pathological research on FTD and Pick's disease.[11] At the meeting, 'FTD' was defined as a clinical term, while 'FTLD' was defined as a pathological term including heterogeneous disorders. Common pathological features of FTLD include neuronal loss with gliosis in the frontotemporal cortices, caudate nucleus and substantia nigra. According to the immunohistochemical classification, FTLD is divided into FTLD with and without tau pathology, and can be further diagnosed by pathological disorders (Fig. 15.1). FTLD without tau pathology is thought to consist mainly of dementia lacking distinctive histopathological features (DLDH); FTLD with MND-type inclusions but without MND (FTLD-MNI); and FTLD with MND. Ubiquitin-positive, tau- and α-synuclein-negative inclusions are typically observed in the neurons of the dentate fascia in both FTLD-MNI and FTLD with MND, but not in DLDH. FTLD-MNI is also known variously as 'FTD with MND-type', 'MND inclusion dementia', 'lobar atrophy without Pick bodies' and 'atypical Pick's disease without Pick

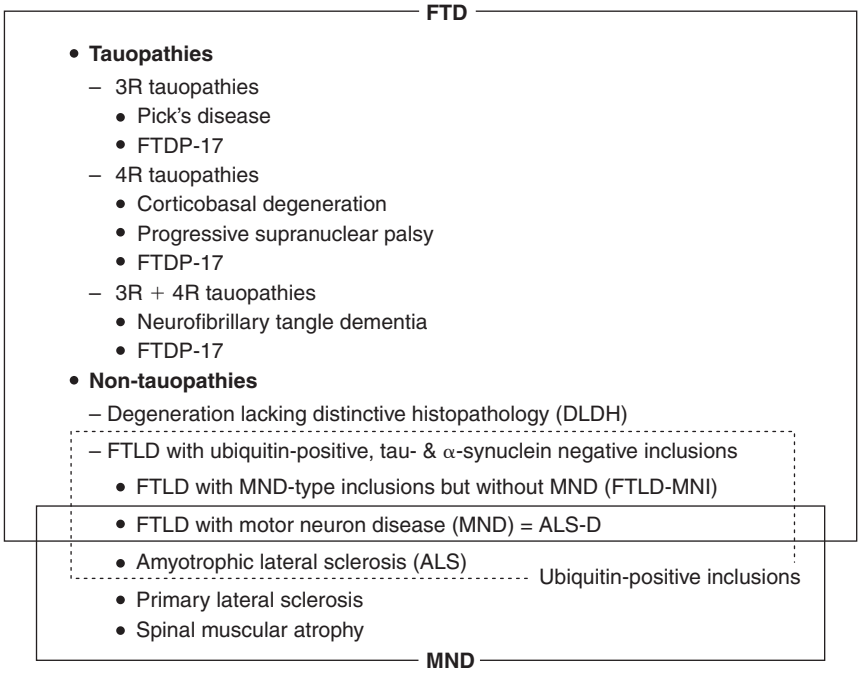

Fig. 15.1 Neuropathological classification of frontotemporal dementia (FTD) and motor neuron disease (MND).

bodies'.[12–15] ALS-D corresponds to FTLD with MND.

ALS

ALS is the most common adult-onset motor neuron disease, which is clinically characterized by progressive weakness and wasting of the skeletal muscles, leading to death from respiratory failure at a median of 3 years after onset. ALS is pathologically characterized by loss of both upper and lower motor neurons such as Betz cells in the motor cortex, motor nuclei in the brainstem and large anterior horn cells in the spinal cord. Degeneration of the corticospinal tract is also a common feature. In addition to these constant features, neuronal inclusions such as Bunina bodies, round hyaline inclusions and skein-like inclusions are hallmarks of ALS.[16–18] Bunina bodies are small eosinophilic granular inclusions on hematoxylin and eosin (H&E) staining in motor neurons. Skein-like inclusions are aggregates of thread-like structures, which are positive for ubiquitin-immunostaining. Ubiquitin-positive inclusions are occasionally detected in the neurons of the hippocampal dentate fascia, neostriatum and frontotemporal cortices.[19–21]

RELATIONSHIPS AMONG ALS-D, FTD AND ALS

The neuropathological classification of FTD and ALS is summarized in Fig. 15.1. ALS-D, FTLD-MNI and ALS could be considered as a disease spectrum with ubiquitin-positive, tau-negative inclusions. Recent studies have revealed some other similarities between ALS, ALS-D and FTD, supporting the theory that they have a common pathogenesis. Recent evidence suggests that cognitive impairments associated with frontotemporal function in patients with ALS are more common than previously described.[22–24]

Corticospinal tract degeneration of Japanese cases with FTLD-MNI

We have reported that Japanese cases with FTLD-MNI exhibit corticospinal tract degeneration, suggesting that FTLD-MNI has a common pathogenesis with ALS.[14] In the present section, we present additional studies of 20 Japanese cases with FTLD-MNI. These cases were collected from the Tokyo Institute of Psychiatry and Yokohama City University of Medicine. The mean age of the cases was 64.9 years, and all were sporadic cases. Clinically, in the later stages of the illness, 9 of the 20 cases presented pyramidal signs, which were sometimes asymmetrical. FTLD-MNI was diagnosed by routine neuropathological examination, revealing neuronal loss and gliosis in the frontotemporal cortices, without degeneration of the lower motor neuron system or Bunina bodies. All cases exhibited mild to severe corticospinal tract degeneration (Fig. 15.2), some of them asymmetrical (Fig. 15.3). Although clinical pyramidal signs were observed in 9 of the 20 cases, pathological corticospinal tract degeneration was found in all 20 cases. These findings indicate that corticospinal tract degeneration is a common feature of FTLD-MNI in Japanese cases, suggesting an overlap between ALS and FTD.

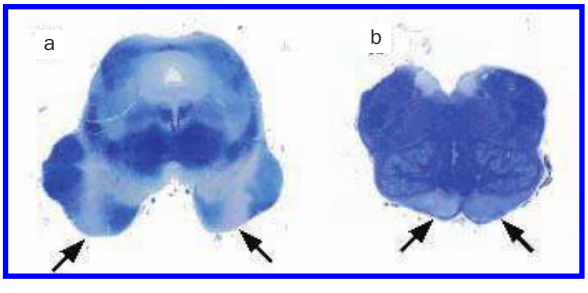

Fig. 15.2 Severe and symmetrical corticospinal tract degeneration. Midbrain (a) and medulla oblongata (b) of a Japanese case with FTLD-MNI. Myelin pallor is seen in both sides of the corticospinal tract (arrows). Kluever-Barrera staining.

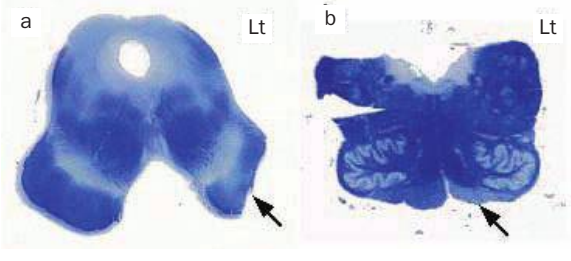

Fig. 15.3 Asymmetrical corticospinal tract degeneration. Midbrain (a) and medulla oblongata (b) of a Japanese case with FTLD-MNI. Myelin pallor is seen in the left corticospinal tract (arrows). Kluever-Barrera staining.

UBIQUITIN PATHOLOGIES OF ALS, FTLD-MNI AND ALS-D

As described above, ALS, FTLD-MNI and ALS-D are pathologically characterized by ubiquitin-positive neuronal inclusions. In these disorders, ubiquitin-positive structures are observed not only in the neuronal cytoplasm but also in the neurites and neuronal nuclei of the cerebrum. It remains unclear, however, whether these ubiquitin-positive structures are the same in each disorder. Therefore, we examined the differences in ubiquitin pathologies and then compared the US and Japanese cases.

Ubiquitin pathology in US cases

Ten brains with ALS (mean age 69.6 years), 47 brains with FTLD-MNI (mean age 70.9) and 3 brains with ALS-D (mean age 58.7) from the Mayo Clinic Jacksonville Brain Bank were studied.[25] Of the 47 cases with FTLD-MNI, 15 had a family history of neurological disease (48.4%) and 16 were sporadic; the family histories of the other 15 cases were uncertain or unavailable. These cases were diagnosed by routine neuropathological studies and immunohistochemistry including ubiquitin, tau, α-synuclein, phosphorylated neurofilament and prion protein (PrP). Ubiquitin pathologies were evaluated in the caudate nucleus and hippocampal dentate fascia, because in these areas there were marked ubiquitin pathologies. The ubiquitin pathologies were divided into some subtypes in each area by their features.

Ubiquitin pathology of ALS in US cases

There were no or only rare ubiquitin-positive neuronal inclusions and neurites in the caudate (Fig. 15.4a) and frontotemporal cortices, but 7 of 10 cases had ubiquitin-positive neuronal pathology in the dentate fascia. The ubiquitin immunoreactivity was granular and did not form a discrete inclusion body (Fig. 15.4b).

Ubiquitin pathology of FTLD-MNI in US cases

Most cases had many ubiquitin-positive neuronal inclusions and neurites in the caudate nucleus and frontotemporal cortices. The ubiquitin pathology in the caudate was characterized by inclusions in medium to small neurons and curvilinear or punctate neuritic processes. Neuronal intranuclear inclusions (NII) were detected in neurons in the caudate nucleus in 26 of the 43 cases. Morphologically, the inclusions were lentiform (Fig. 15.4c), rod-shaped or round in shape, and observed most often in medium and small neurons. Although NII were originally reported in familial cases, NII were observed even in our sporadic US cases.[25,26] Most cases had ubiquitin-positive neuronal inclusions in the hippocampal dentate fascia. There was a range of morphologies in these inclusions, including round, Pick body-like inclusions, crescent or ring-shaped inclusions

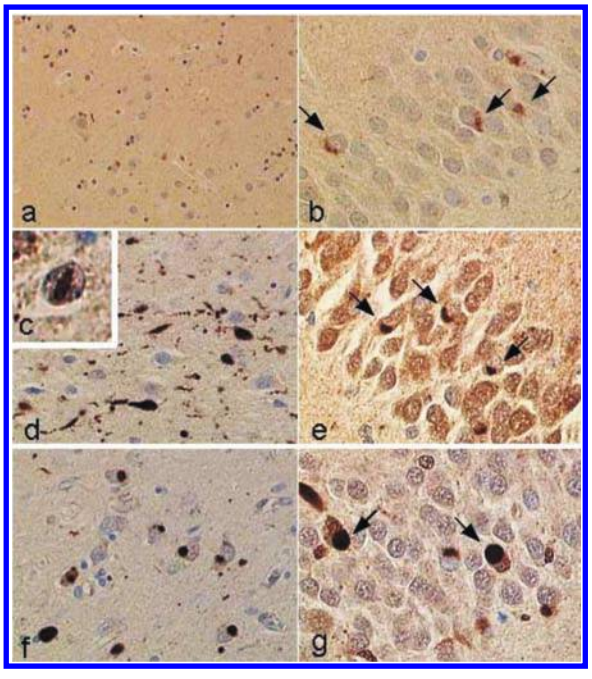

Fig. 15.4 Immunohistochemistry ubiquitin. (a, b) A US case with ALS. (a) A few ubiquitin-positive neuronal inclusions and neurites in the caudate nucleus. (b) Granular perikaryal ubiquitin-positive inclusions (arrows) in the dentate fascia. (c–e) A US case with FTLD-MNI. (c) Ubiquitin-positive lentiform neuronal intranuclear inclusion in the caudate nucleus. (d) Many ubiquitin-positive neurites in the caudate nucleus. (e) Ubiquitin-positive crescent-shaped neuronal inclusions (arrows) in the dentate fascia. (f,g) A Japanese case with FTLD-MNI. (f) Many ubiquitin-positive neuronal inclusions in the caudate nucleus. (g) Ubiquitin-positive Pick body-like neuronal inclusions (arrows) in the dentate fascia.

and granular cytoplasmic staining without a well-defined structure. The ubiquitin pathologies in the caudate nucleus and dentate fascia were interrelated. Although the ubiquitin pathologies of FTLD-MNI in our US cases were heterogeneous, the most common familial ubiquitin pathology (US type) was predominant neuritic pathology (Fig. 15.4d) with NII in the caudate nucleus and crescent neuronal inclusions (Fig. 15.4e) in the dentate fascia.

Ubiquitin pathology of ALS-D in US cases

Our US cases with ALS-D had only a few or no ubiquitin-immunopositive lesions in the caudate nucleus and frontotemporal cortices, but all three had ubiquitin-positive neuronal pathology in the dentate fascia and most were of granular appearance. No Pick body-like, crescent or ring-shaped inclusions were detected. The ubiquitin pathology of ALS-D in our US cases was similar to that of ALS, but different from that of FTLD-MNI.

Interrelationship between ALS, FTLD-MNI and ALS-D in US cases

Figure 15.5 shows the interrelationship between ALS, ALS-D and FTLD-MNI in our US cases. ALS and ALS-D are characterized by mild ubiquitin pathology in the caudate and granular neuronal inclusions in the dentate fascia. In contrast, FTLD-MNI is characterized by severe neuritic ubiquitin pathology with NII in the caudate and crescent-shaped neuronal inclusions in the dentate fascia.

Ubiquitin pathology in Japanese cases

Nineteen cases with ALS (mean age: 61.1 years), 20 cases with FTLD-MNI (mean age 64.9) and 7 cases with ALS-D (mean age 64.4) were collected from the Tokyo Institute of Psychiatry and Yokohama City University of Medicine. All cases were sporadic, unlike the US cases. The pathologies of the Japanese cases were evaluated in the same way as the US cases.

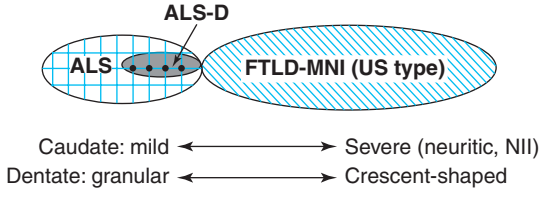

Fig. 15.5 Interrelationship between ALS, FTLD-MNI and ALS-D in US cases.

Ubiquitin pathology of ALS in Japanese cases

In the caudate, ubiquitin-positive neuronal inclusions and neurites were rare. In the dentate fascia, 10 of the 19 cases had ubiquitin-positive granular neuronal inclusions. These features are similar to the US cases.

Ubiquitin pathology of FTLD-MNI in Japanese cases

The ubiquitin pathology of FTLD-MNI in our Japanese cases was different from the US cases. Most had severe neuronal inclusion-dominant pathology (Fig. 15.4f), but no NII, in the caudate nucleus and Pick body-like neuronal inclusions (Fig. 15.4g) in the dentate fascia (Japanese type).

Ubiquitin pathology of ALS-D in Japanese cases

The ubiquitin pathology of ALS-D in the Japanese cases exhibited characteristics intermediate between ALS and FTLD-MNI. In the caudate nucleus, there were rare or occasional ubiquitin-positive neuronal inclusions and neurites. In the dentate fascia, four of the seven cases had granular neuronal inclusions, and three had Pick body-like neuronal inclusions.

Interrelationship between ALS, FTLD-MNI and ALS-D in Japanese cases

Figure 15.6 shows the interrelationship between ALS, FTLD-MNI and ALS-D in our Japanese cases. ALS is characterized by mild ubiquitin pathology in the caudate and granular neuronal inclusions in the dentate fascia. FTLD-MNI is characterized by severe neuronal ubiquitin pathology in the caudate and Pick body-like neuronal inclusions in the dentate fascia. The ubiquitin pathology of ALS-D is characterized as intermediate between ALS and FTLD-MNI.

Spectrum of FTD/ALS from the perspective of ubiquitin pathology (Fig. 15.7)

In conclusion, from the perspective of ubiquitin pathology, there are no differences in ALS cases between the USA and Japan. On the other hand, FTLD-MNI includes two different types: the US type and the Japanese type. These findings still suggest that FTLD-MNI is heterogeneous, and the differences may be related to unknown genetic factors.

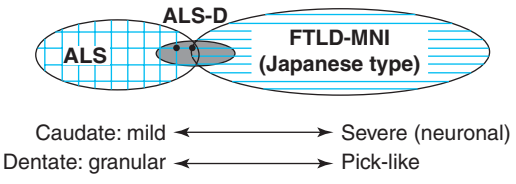

Fig. 15.6 Interrelationship between ALS, FTLD-MNI and ALS-D in Japanese cases.

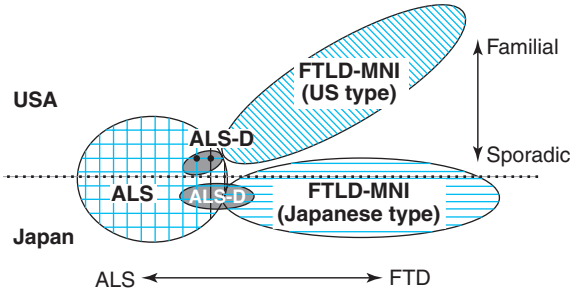

Fig. 15.7 Spectrum of FTD/ALS from the perspective of ubiquitin pathology.

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The genetics of frontotemporal dementia

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INTRODUCTION

Frontotemporal dementia (FTD) is the second or third most common cause of dementia after Alzheimer's disease, and Lewy body dementia if that is classified separately from Alzheimer's disease. It is a syndrome with several different forms: each of these has different underlying pathologies and presumably different underlying etiologies, and these etiologies and pathogeneses have relationships with other diseases. In this chapter, we will discuss the following types of FTD:

1. FTD with parkinsonism linked to chromosome 17 with tau mutations (FTDP-17T, OMIM: 600274).

   This is the best characterized form of the disease and seems to share pathogenic relationships – especially with progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). It shares some features with Alzheimer's disease and may share some pathogenic mechanisms with Parkinson's dementia complex of Guam. These latter diseases will also be briefly discussed in this context.
2. FTD with parkinsonism linked to chromosome 17 without tau mutations (see FTDP-17U, OMIM: 600274).

   A proportion of cases linked to chromosome 17 do not have tau pathology and do not have MAPT mutations. Many, perhaps all, of these cases have ubiquitinated inclusions and may share pathogenic relationships with FTD/ALS cases or with dementia with Paget's disease (see below). It is remarkable that this disease, which seems clinically indistinguishable from FTDP-17T, maps to the same locus but has a different pathology from this latter disorder. Clearly there has been extensive analysis of the MAPT locus in this disease, and in fact the adjacent *NSF* gene is an equally good candidate because it has extensive homology to the *VCP* gene which is the cause of dementia with Paget's disease (see below). However, no mutations have yet been found.
3. FTD linked to chromosome 3 (OMIM: 600795).

   A single family from Denmark showing linkage to this locus has been reported and recently a mutation in the *CHMP2b* gene has been identified in this pedigree. This is clearly a rare disorder given that no other families have been reported to show linkage to the same locus.
4. Neuronal intermediate filament inclusion dementia.

5. FTD with presenilin mutations.
6. Dementia with neuroserpin inclusions (OMIM: 604218).
7. Dementia with bony cysts (OMIM: 221770).
8. Dementia with Paget's disease (OMIM 167320).
9. Dementia with amyotrophic lateral sclerosis (ALS-FTD).

We will not specifically review either prion disease or Alzheimer's disease, although these can occasionally give rise to a FTD phenotype.

FTD WITH PARKINSONISM LINKED TO CHROMOSOME 17 WITH TAU MUTATIONS (OMIM: 600274)

The known role of the tau gene is to stabilize microtubules. It has a long N-terminal of unknown structure and then four microtubule binding domains encoded by exons 9, 10, 11, and 12. Alternate splicing of exon 10 generates either four repeat (4R) tau (exon 10 in) or three repeat (3R) tau (exon 10 out). In normal adult brains, about half of all transcripts are 3R and half are 4R.

Of all the frontal dementias, this is the best characterized, with currently 34 published, fully penetrant mutations[1,2] (http://www.molgen.ua.ac.be/ADMutations/default.cfm?MT=3&ML=1&Page=Contact). These mutations can be essentially divided into four types:

a. Mutations that increase exon 10 splicing in and result in more 4R tau being produced.
b. Point mutations in exon 10.
c. Point mutations in other microtubule binding domains.
d. Point mutations close to the N terminal.

While this is an oversimplification, in general, those mutations which alter exon 10 splicing lead to the deposition of wispy filaments of 4R tau. Point mutations in exon 10, in general, lead to the deposition of mutant 4R tau. Point mutations elsewhere in the microtubule binding domains or in exon 1 lead to the deposition of both 3R and 4R tau (although there are exceptions to this).[3] The precise mechanism by which mutations are pathogenic is not quite clear: either the mutant forms are more prone to aggregation or they bind tubulin less effectively and thus 'fall off' microtubules more readily and then aggregate.[4] While both suggestions may hold part of the truth, the exon 1 mutations are in a domain that is believed to inhibit microtubule binding by folding back and masking the microtubule binding domains.[5]

The clinical phenotype of FTDP-17T is very variable and is not yet predictable from the mutation, although the variability within families is less than the variability between different families with the same mutation, which is less than the variability between families with different mutations. Motor neuron involvement occurs with some families.[6] There is some evidence that the tau haplotype influences the phenotype.[7] Some cases of FTDP-17T clinically and pathologically resemble CBD and PSP: more generally, though, these sporadic diseases show an association with the MAPT haplotype.[8,9] This association suggests that genetic variability in expression or splicing at the MAPT locus contributes to the risk of these tangle disorders. More recent and more detailed analysis of the MAPT locus has suggested that this association may be a more general phenomenon in all tangle disorders including Alzheimer's disease and Parkinson's dementia complex (PDC) of Guam[10–12] although this remains to be confirmed.

FTD WITH PARKINSONISM LINKED TO CHROMOSOME 17 WITHOUT TAU MUTATIONS (SEE OMIM: 600274)

It is surprising that several families which showed linkage to chromosome 17 did not have mutations in the MAPT locus: indeed, one of the reasons that it took so long to move from linkage to the *MAPT* gene mutants was that some critical families did not harbor such mutations.[13] Several families have been reported.[14–16] These families have less prominent or possibly no tau pathology and many or all cases have ubiquitinated inclusions.[16] This pathology resembles the pathology of dementia with bone cysts (OMIM 221770) in which mutations in valosin-containing protein (VCP) have been described (see below). Adjacent to MAPT is the *NSF* gene which is homologous to the *VCP* gene: however, so far no mutations in *NSF* have been found. Thus the etiology of this disease remains a

mystery, as does the coincidence of its genetic localization so close to the *MAPT* gene.

FTD LINKED TO CHROMOSOME 3 (OMIM: 600795)

A genetic linkage to chromosome 3 was identified in a single Danish family with 11 sampled affected individuals (FTD-3) in which histopathological examination shows no distinct features except very mild tau pathology.[17–19] Recently, a mutation in the *CHMP2b* gene has been identified which segregated with disease in this family.[20] Extensive sequencing of other FTD cases failed to identify other mutations;[20] however, the authors have recently identified a similar, though not identical, mutation in a sample from an unaffected individual, making the status of pathogenicity of *CHMP2b* mutations uncertain at present.

NEURONAL INTERMEDIATE FILAMENT INCLUSION DEMENTIA (NIFID)

NIFID is a neurological disease with a clinically heterogeneous phenotype including progressive early-onset FTD, pyramidal and extrapyramidal signs,[21] with only 10 cases reported to date. The most common symptoms are behavioral and personality changes and memory loss, cognitive impairment, language deficit, perseveration, motor weakness, and to a lesser extent, executive dysfunction. Macroscopic manifestations include atrophy of the frontal lobe and less so, temporal and parietal lobes.[22] Due to clinical heterogeneity, histopathology is a solid basis for the classification of disease. Microscopically, there are intraneural, cytoplasmic neuronal granular inclusions in subcortical nuclei and spinal cord, which are tau- or α-synuclein-negative but are variably ubiquitinated. The signature lesions of cytoplasmic lesions are neuronal intermediate filaments, α-internexin and neurofilament subunits. Half of the reported cases also have highly ubiquitinated neuronal intranuclear inclusions,[23] which unlike cytoplasmic inclusions contain no α-internexin or neurofilament subunits. A complete mutational analysis of α-internexin and neurofilament genes has not shown any pathogenic variants.[24]

FTD WITH PRESENILIN MUTATIONS

It is clear that presenilin mutations usually cause Alzheimer's disease[25] (http://www.molgen.ua.ac.be/ADMutations/default.cfm?MT=3&ML=1&Page=Contact) and also that Alzheimer's disease can rarely present as a frontotemporal syndrome (e.g. Rippon et al.[26]). However, what is more interesting but less well characterized, is the possibility that presenilin mutations may cause FTD in the absence of amyloid pathology. Two families have been described[27,28] in which presenilin mutations seem to result either in no distinctive histopathology[27] (B. Boeve, personal communication) or in tangle pathology.[28] The mutations found in the family without distinctive pathology were shown to completely block presenilin's γ-secretase activity *in vitro*, which might provide a clue as to the mechanism of pathogenesis.[29] However, there has been no demonstrated segregation in this family, making a definitive assessment of its pathogenicity suspect.

DEMENTIA WITH NEUROSERPIN INCLUSIONS (OMIM: 604218)

The causes of this rare disorder are mutations (two described so far) in the neuroserpin gene. These mutations lead to the deposition of neuronal inclusions of neuroserpin. These inclusions resemble inclusions in the liver seen in antitrypsin deficiency and presumably share pathogenic mechanisms with this disorder since antitrypsin is a serpin.[30]

DEMENTIA WITH BONE CYSTS (OMIM: 221770)

This is an extremely unusual disorder with a combination of bone cysts, often presenting as fractures, and a progressive early-onset dementia which can resemble Alzheimer's disease clinically. It seems likely that this disease is underdiagnosed because, while the original descriptions of the disease have come from Finland and Japan where there is a higher prevalence of the disease due to founders, nearly all subsequent cases have come from Scandinavian centers with a knowledge of the disorder

because of their proximity to Finland, suggesting that unrecognized cases are occurring in other countries. Recessive loss of function mutations in two genes have been shown to be responsible for this disorder, *TYROBP* and *TREM2*. In a *tour de force*, Paloneva and colleagues[31,32] showed that the two cognate proteins of these genes were different subunits of the same signaling complex, largely explaining the similarity between the two genetic forms of the disease.

DEMENTIA WITH PAGET'S DISEASE (OMIM 167320)

This too, is a complex, though apparently rare and autosomal dominant disease, with dementia, myopathy and Paget's disease as symptoms, but to differing extents in different individuals even within the same family.[33,34] Missense mutations in the valosin-containing protein are the cause of this disease, which is characterized by intraneuronal inclusions consisting of ubiquitinated VCP.[35,36] These inclusions, superficially at least, resemble the ubiquitinated inclusions in FTDP-17U (see above), suggesting that there might be a pathogenic relationship between these two diseases. Interestingly, *NSF*, a gene with high homology to *VCP*, lies in the linkage candidate region for FTDP-17U, but no segregating mutations have been found.

DEMENTIA AND ALS

Conventionally, ALS has been considered to be a disease characterized by the selective degeneration of motor neurons giving rise to progressive paralysis, respiratory failure and ultimately death. Recent clinical and pathological research suggests that ALS is a more widespread disease affecting extramotor neuronal systems and that ALS, ALS-FTD and FTD form a spectrum of disease that differs only in the extent and distribution of a common pathology characterized by ubiquitinated inclusions.[37,38] Ubiquitinated inclusions are almost universal in ALS and its variants.[39] They are composed of 10 μm diameter filaments that can only be reliably detected by ubiquitin immunocytochemistry and again superficially resemble those found in dementia with Paget's disease.[40]

About 5% of ALS patients have FTD (ALS-FTD).[41] Additionally it is now recognized that at least half of patients with 'classic' ALS have mild cognitive impairment that is distinct from the overt dementia seen in ALS-FTD.[42–44] Cognitive dysfunction usually follows the onset of neuromuscular deficits and manifests as subtle defects in frontal and temporal lobe functions. The pattern of neuropathology is similar in ALS patients without cognitive impairment, ALS patients with cognitive impairment and ALS-FTD patients, namely the presence of ubiquitinated inclusions in the hippocampal dentate cells, the superficial frontal and temporal cortex and the entorhinal cortex. Instead, the main difference between these groups lies in the load of cortical lesions, with the largest number of ubiquitinated inclusions being found in ALS-FTD patients, the least in ALS patients without cognitive impairment, and ALS patients with mild cognitive impairment having an intermediate number.[45]

On the opposite end of the disease spectrum are patients with apparently 'pure' FTD. This view is rapidly being challenged. Clinical involvement of the motor system was observed in half of a large series of FTD patients with no known diagnosis of ALS.[46] Ubiquitinated inclusions have been found in a portion of FTD cases where spinal cords were examined,[47] leading some authors to suggest that these cases define a unique subset of FTD confusingly called motor neuron disease inclusion dementia.[48] However, the true incidence of this subclassification has not been quantified, because the spinal cords of FTD patients are not routinely examined.

In summary, there is considerable clinical and pathological evidence to suggest that ALS, ALS-FTD and FTD represent different morphological expression of a specific molecular phenotype and that the difference in phenotype can be explained by the distribution and load of the ubiquitinated inclusions in the CNS.

While mutations of the Cu/Zn superoxide dismutase gene (*SOD1*) account for approximately a quarter of familial ALS cases, these are infrequently associated with dementia and the

ubiquitinated inclusions mentioned above are rarely seen. Linkage of ALS-FTD to both chromosome 9p and 9q have been reported, but these genes have not yet been identified.[49,50]

CONCLUSIONS

In the last 10 years, through genetic analysis, we have begun to make real progress in understanding the etiology of FTD, and there has been parallel progress in the development of our understanding of ALS. The tauopathies are clearly one large family of diseases and work on these is progressing rapidly. For the rare diseases, reviewed above, progress will undoubtedly be slow because of the limited resources which will be devoted to their understanding. However, there seems to be one large group of diseases which is emerging from the shadows, which includes those diseases with a spectrum of ALS and dementia and with ubiquitin inclusions. Perhaps these will share pathogenic mechanisms with the VCP-encoded disease. When other genes which cause Mendelian versions of this spectrum of diseases are discovered, we will be able to see whether, in addition to the tangle (and Lewy body, and polyglutamine inclusion) routes to cell death, there is another major pathogenic process leading to these interesting but devastating diseases.

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Frontotemporal dementia and the involvement of tau

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FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia (FTD) is considered to be the second most common form of primary degenerative dementia after Alzheimer's disease (AD).[1–3] FTD represents up to 20% of presenile dementia cases.[2] Disease onset is usually in middle age between 45 and 65 years; however, there can be considerable variation (< 30 to > 80 years). The duration of disease also varies and can be from 2 to 20 years. The incidence of FTD in men and women is approximately equal. Significantly, a large proportion of FTD patients (35–50%) have a family history of dementia, suggesting a large genetic contribution to the etiology of this disease.[4–6] Clinically, FTD is characterized by profound behavioral and personality changes with relative preservation of perception and memory. A parkinsonism syndrome can develop in certain patients as the disease progresses, although this is normally absent at onset, and around 10–15% of cases display clinical features of both FTD and amyotrophic lateral sclerosis (ALS).[1,7,8]

FTD and parkinsonism linked to chromosome 17 (FTDP-17)

FTD with parkinsonism linked to chromosome 17 (FTDP-17)[9] is a term now commonly used to describe familial FTD that results from mutations in the gene for the microtubule-associated protein tau. Generally, the clinical features of FTDP-17 are consistent with idiopathic FTD. At autopsy, patients with FTDP-17 exhibit frontotemporal atrophy with neuronal loss, gray and white matter gliosis and superficial cortical microvacuolation. Importantly, all reported cases of FTDP-17 have prominent intraneuronal tau inclusion pathology, with glial tau inclusions observed in some families.[10–12] However, the morphology and isoform composition of the tau filaments that compose the inclusions is highly variable. Certain FTDP-17 families display intraneuronal spherical tau inclusions (Pick bodies) and tau-positive swollen neurons (Pick cells) consistent with a neuropathological diagnosis of Pick's disease, while other FTDP-17 families develop neurofibrillary tangle (NFT) lesions that are identical to those observed in Alzheimer's disease (AD).[13–18]

The identification of missense[19,20] and splice site mutations[17,19] in the gene for tau in FTDP-17 was a highly significant discovery, as it finally demonstrated that tau dysfunction alone is sufficient to cause neurodegeneration. This was important because tau inclusions are a major neuropathological feature of many neurodegenerative conditions.[21] The discovery of tau mutations in FTDP-17 suggests that the

neurobiological dysfunction of tau could have a pathogenic role in other 'tauopathies'. In the normal brain tau binds to microtubules and is thought to regulate the dynamic behavior, assembly, and spatial organization of the neuronal microtubule network.[22,23] In the adult human brain tau exists as six isoforms (Fig. 17.1) generated by alternative splicing (exons 2, 3, and 10).[24,25] The interaction between tau and tubulin is via four imperfect repeat domains (31–32 residues) encoded by exons 9–12.[26] Alternative splicing of exon 10 gives rise to isoforms with three (exon 10–) or four (exon 10+) binding domains (3R and 4R tau)[25] (Fig. 17.1). In the normal adult brain this ratio of 3R and 4R isoforms is approximately equal.

Since the original reports in 1998 describing tau mutations associated with FTDP-17, over 30 different mutations have been identified in more than 80 families.[10] These account for 10–15% of familial FTD cases, although this proportion is higher if analysis is restricted to cases in which an autopsy has shown the presence of prominent tau pathology.[27–29] Mutations of tau include 19 missense mutations, 2 deletions (ΔN296 and ΔK280), 3 silent mutations in exon 10 and 7 mutations in the intronic sequence proximal to the 5′ splice site of exon 10 (Fig. 17.2). All of these mutations apart from two in exon 1 (R5L, R5H)[30,31] affect exons 9–13, which encode the carboxy-terminal portion of tau, including the microtubule binding repeats (exons 9–12).

Mutations associated with FTDP-17 generally have one of two effects (Fig. 17.2). The first type (missense and deletion mutations) alters the protein sequence and its function such that the interaction between tau and the microtubule is either decreased[32–34] or increased.[15] Furthermore, some of these mutations also increase the tendency of tau to aggregate into filaments, *in vitro* and *in vivo*.[15,16,35] The accumulative result of these mutations appears to lead to an overall increase in the rate of formation of tau neurofibrillary lesions. However, the exact mechanism by which the effects of these mutations lead to neurodegeneration and to FTDP-17 is uncertain. The second type of mutation does not alter the protein sequence but rather disrupts the alternative splicing of exon 10.[17,19,36] These types of mutations alter cis-acting splice regulatory element in exon 10 or in the intron proximal to the 5′ splice site.[37–40] Many of these mutations affect recognition of the 5′ splice site.[19,37] This leads to a disruption of the exon 10 splicing regulatory sequences, causing the proportion of exon 10+ to 10– tau RNA to be dramatically altered and hence the proportion of 4R to 3R tau is shifted.[17,19] This shift in the ratio of 4R and 3R tau isoforms appears sufficient to cause neurodegeneration in FTDP-17. While these splicing mutations demonstrate the importance of the 4R:3R tau isoform ratio, it remains unclear how the disruption of this ratio eventually results in neurodegeneration.

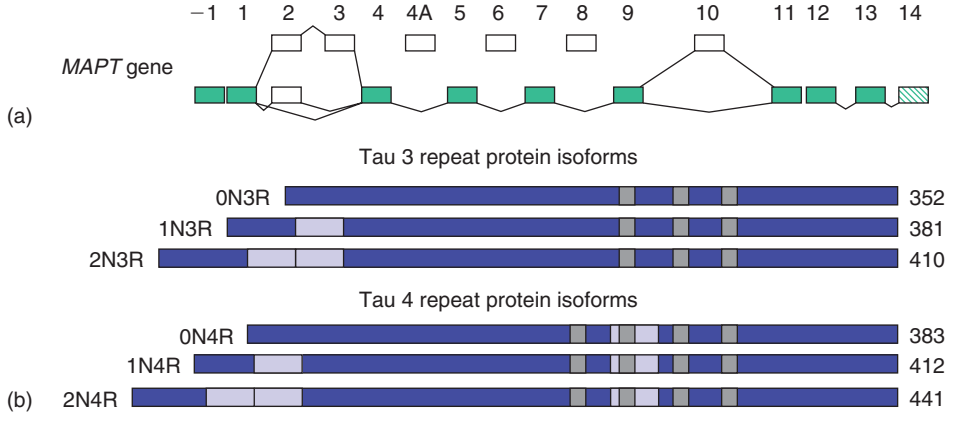

Fig. 17.1 The tau gene and splicing. (a) A diagram of the tau gene structure showing exons that are alternatively spliced in adult human brain. (b) Diagram of the protein isoforms expressed in adult human brain, indicating the nomenclature and number of amino acid residues in each isoform. Microtubule binding repeats are shown as gray bars.

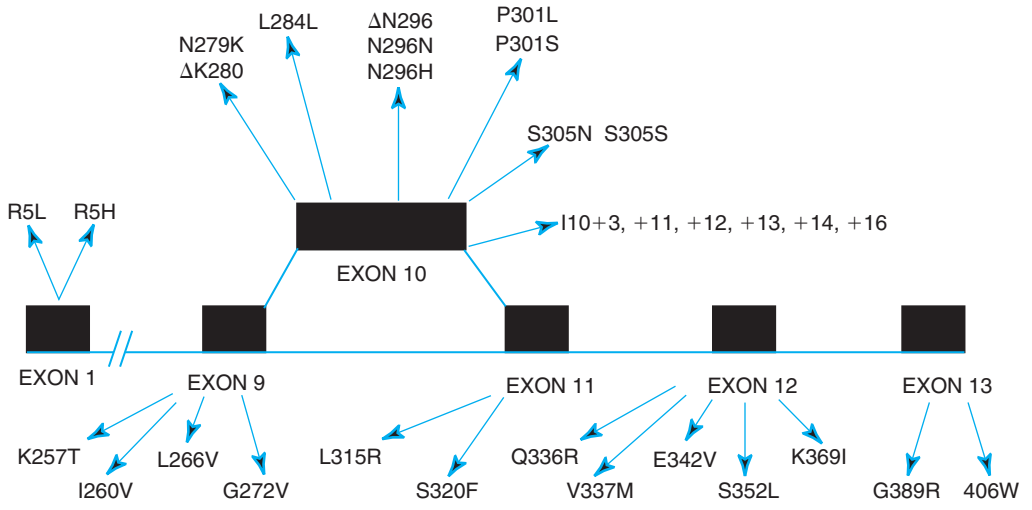

Fig. 17.2 Tau mutations in FTDP-17. A diagram of the tau gene showing the location of mutations reported to date. Intronic mutations are denoted by the nucleotide position of the mutation relative to the 5′SS of exon 10.

The identification of mutations in *tau* has partly explained the variability in the tau pathology observed in FTDP-17. Individuals with mutations in exon 10 that affect the microtubule binding properties of 4R tau (e.g. P301L/S) or that increase the 4R:3R tau isoform ratio (e.g. N279K, S305N) display a neurofibrillary pathology that consists predominantly of 4R tau.[17,18,34] These inclusions consist of filaments that are variable but have a different morphology, and often a longer periodicity, than the paired helical filaments (PHFs) observed in the neurofibrillary tangles of AD. Mutations of this type lead to prominent tau pathology in glia in addition to neurons. In addition, pathological lesions resulting from mutations in exons 9, 11, 12 and 13 that affect both 4R and 3R isoforms present with a morphology of usually either that of Pick-like bodies[13–15,41] or NFT with PHFs similar to those observed in AD.[18] The presence of tau inclusions in glia is also more variable with these mutations.

Chromosome 17-linked tau-negative FTD + ALS

Almost all families with FTD and linkage to chromosome 17 have mutations in the tau gene. However, there is a subset of FTD families which are linked to the same region of chr17q21 but despite extensive analysis mutations in tau cannot be found.[42–47] Importantly, in contrast to the FTDP-17 families with mutations in tau these families are also characterized by the absence of tau pathology. Six families of this type have been described to date. Three of these families are conclusively linked to chromosome 17 with maximum LOD score of 3.46, 3.68 and 5.51.[45–47] The published minimal candidate region for this locus is a 5.3 Mb interval between D17S1787 and D17S958 (5 cM) that includes the tau gene.[46] It is possible that an unusual tau mutation in an intron or regulatory sequence or a chromosomal abnormality affecting the tau gene might yet be found in these families. However, following haplotype analysis in the family described by Kertesz et al.[44] a tentative recombination event within the tau gene (in intron 9) is reported. This would exclude the 3′ end of tau; however, the maximum LOD scores in this family were below 2 and thus interpretation of this recombinant individual needs to be treated with caution.[42] Nevertheless, this recombinant would not exclude the 5′ end of the *tau* gene as a potential site for the pathogenic mutations.

The clinical phenotype in each of these families is characterized by a presentation consistent with criteria for FTD[1–3] with a variable age of onset (38–79 years) both within and between families.[42–47] Early or late extrapyramidal motor

dysfunction can be present in some patients. The neuropathological features observed are similar to the microvacuolar-type pathology seen in the majority of FTD cases with spongiform change in the neuropil of the superficial cortical layers.[48] Importantly, prominent extramotor ubiquitin-positive, tau-negative inclusions have been reported in three of these families.[43,45–47] These ubiquitin-positive neuronal inclusions are found in layer II of the cortex and in the dentate gyrus of the hippocampus and in this respect are similar in appearance and distribution to those described in FTD with ALS.[49,50] The majority of these inclusions are found in the neuronal cytoplasm; however, small intranuclear ubiquitin-positive lentiform inclusions in some neurons are reported in certain families.[43,46,47] Whether these intranuclear inclusions have been missed, due to their small size and low frequency, in the other tau-negative families remains to be established. Nevertheless, these intranuclear inclusions do not react against an antibody to polyglutamine tracts, making it unlikely that these are caused by a tri-nucleotide repeat expansion mutation.[47] Anticipation, the reduction and/or increasing in disease severity in successive generations, is also not observed in these families.

This subgroup of tau-negative FTD families linked to chr17q21 are an important group because identification of the genetic cause of disease in these cases will provide information on the etiology of tau-negative FTD and FTD-ALS. The linkage to the same region of chr17q21 that harbors the tau gene is intriguing given that no obvious tau mutations have been identified so far in these families. This raises the possibility that a mutation deep in an intron or in regulatory regions may yet be discovered. Alternatively, a large-scale genomic rearrangement of the tau locus could be pathogenic in these families. It is interesting that a recently reported tau-splicing mutation (E10 5'SS +29), that increases 3R tau, was also associated with a tau-negative neuropathology.[51] The pathogenic nature of the change needs to be treated with caution as Stanford and colleagues also found it in control subjects.[51] Nevertheless, the extensive analysis of the tau gene in chr17q21-linked tau-negative FTD families argues against tau being responsible for disease. This suggests the possibility that another gene lies in this region causing familial FTD. It is worth noting that this particular region of chr17q21 is particularly gene-rich and harbors one other gene, i.e. glial fibrillary acidic protein (GFAP), that causes the neurodegenerative disease known as Alexander's disease.[52] Nevertheless, if the *tau* gene is mutated in these families it will be important to determine how this leads to disease and neurodegeneration in the absence of the accumulation of insoluble tau aggregates.

CLEARANCE MECHANISMS OF TAU AND RELEVANCE TO TAUOPATHY

Aggregation of tau has long been thought to be a deleterious consequence of abnormal tau metabolism, with most research focusing on the role of aberrant phosphorylation[53,54] and conformational changes[55] that lead to dissociation from microtubules and formation of stable aggregates. Neurofibrillary pathology may be harmful by sequestering tau protein that is vital to polymerization and stability of microtubules, which are crucial to a number of normal cellular functions/activity, including axoplasmic transport. In addition, soluble abnormal tau species may have direct toxic effects and may contribute to neuronal apoptosis. One mechanism for this cellular injury may arise through their effects on over-burdened or malfunctioning protein degradative systems that leave cells with no means for removal of these toxic species.[56,57] In this situation, tau partitioned into aggregates is an adaptive cellular response that prevents ill effects of aberrant soluble tau proteins. In support of this idea is the recent evidence that suppression of mutant tau expression in inducible tau transgenic mice, at an age when neurofibrillary tangle pathology and memory deficits are manifest, resulted in rescue of cognitive defects without altering neurofibrillary pathology.[58] This further suggests that formation of tau aggregates may not be the primary mechanism linking tau pathology to neuronal death.

Accumulation of abnormally phosphorylated forms of tau protein in tauopathies and models of these diseases has been attributed to enhanced tau expression,[59] expression of mutant forms of

tau with inherent tendency to aggregate,[60] increased activity of kinases,[61] and reduced activity of phosphatases.[62] However, based on our work and that of others,[63,64] abnormalities in clearance of tau may be equally culpable. A role for the ubiquitin proteasome system (UPS) in the removal of aberrant tau species was suggested by studies demonstrating that proteasome-dependent degradation of constitutive heat shock protein 70 (Hsp70)-bound phospho-tau was specifically facilitated by the chaperone CHIP (carboxyl terminus of the Hsp70-interacting protein) through direct E3 ligase poly-ubiquitination activity[63,64] (Fig. 17.3). Recently, several components of the UPS have been implicated in the removal of other aggregation-prone proteins implicated in neurodegenerative disorders.[65,66] CHIP and HSP27 facilitate ubiquitin-dependent and ubiquitin-independent degradation of tau, respectively.[64,67–69]

Proteolysis is a critical mechanism for maintaining the intracellular environment relatively free of misfolded/aberrant proteins[68] and for the most part this function is carried out predominantly by the ubiquitin/proteasome system.[68] The covalent ligation and modification of substrate with multiple ubiquitin molecules targets the ubiquitinated protein to the 26S proteasome. The unfolded substrate is then threaded into the inner core of the 20S subcomplex and proteolytically cleaved.[70] Often this pathway to the proteasome requires a collaboration between the ubiquitin–proteasome and chaperone systems such as CHIP and Hsp70.

Proteasomal dysfunction is believed to contribute to a variety of human neurodegenerative diseases.[68] For many of the intracellular lesions (cytoplasmic or nuclear) the evidence of degradative systems is cursory and generally consists of a ubiquitinated inclusion, sometimes in complex with other chaperones/ligases, and the obvious detail that the inclusions failed to clear.[71] In the case of tauopathies, neurofibrillary tangles cannot be easily degraded[72] and their toxicity is enhanced in cell culture systems and *in vivo* models.[58,64] What is known is that mutations in tau can lead to intracellular inclusions and cellular dysfunction. This pathological observation leads to several unanswered questions in the field: at what point in the pathogenic cascade (i.e. monomer, oligomeric, aggregrated) that begins with mutant tau is there an interface with the degradative machinery? How does the UPS either worsen or ameliorate the inclusions and ultimately the toxicity?

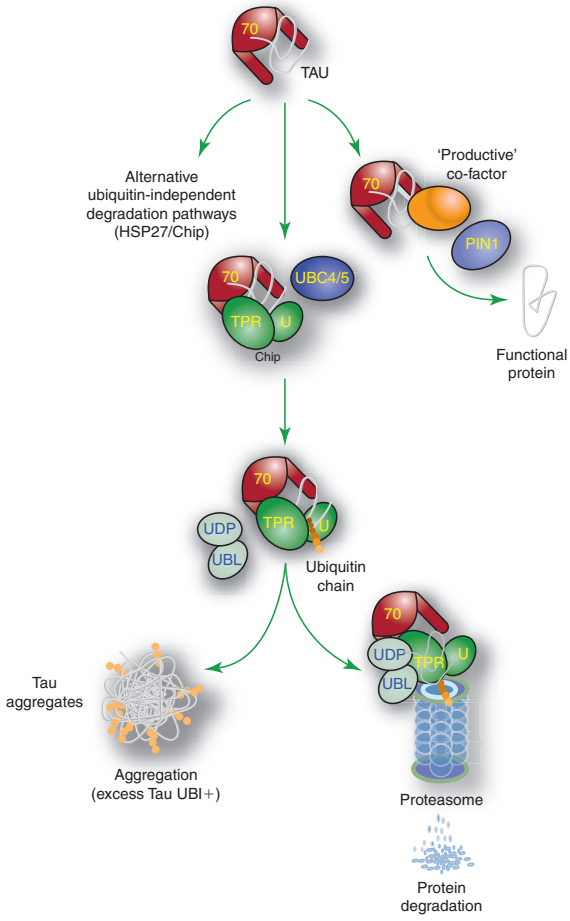

Fig. 17.3 Tau degradation pathway via the UPS. A diagram summarizing tau triage decision by the ubiquitin–proteome system. (Our thanks to Jason Eriksen for supplying the graphic.)

CONCLUSION

Considerable progress has been made over the past decade in unravelling the genetics of FTD and the role of tau in neurodegeneration. The identification of mutations in tau revitalized the tau field by finally demonstrating that tau dysfunction can lead directly to neurodegeneration. From this, considerable progress has been made

in the understanding of mechanisms underlying tau metabolism in normal and pathological states. There are more genetic causes of FTD yet to be identified and hopefully once found these will expand our understanding of the molecular etiology of FTD and the involvement of neuronal inclusions in neurodegeneration.

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18

Altered tau protein metabolism in amyotrophic lateral sclerosis with cognitive impairment

Michael J Strong and Wencheng Yang

INTRODUCTION

The association of amyotrophic lateral sclerosis (ALS) or more anatomically restricted forms of motor neuron disease (MND) with a frontotemporal dementia (FTD) is increasingly recognized. Once held to be a disorder restricted to the motor system, it is now clear that in a proportion of patients with ALS there can be an associated cognitive, behavioral or dysexecutive syndrome, sharing many of the neuropathological features of the frontotemporal lobar degenerations (FTLDs) – many of which are associated with alterations in tau protein metabolism. In some instances, a florid FTD, meeting all of the Neary criteria,[1] can either precede the onset of motor deficits or occur concurrently. In other instances, the FTLD occurs concomitantly with the neuropathological lesions of ALS, including the presence of ubiquitin immunoreactive intraneuronal aggregates within spinal cord and brainstem motor neurons, but in the absence of ante-mortem evidence of ALS. These observations suggest that there exists a considerable clinical and neuropathological spectrum of ALS and ALS-FTD/FTLD. In this chapter, we will examine the role of altered tau metabolism in ALS and its contribution to this spectrum.

FTD, FTLD AND ALS: TERMINOLOGY

To some extent, understanding the basis of the cognitive dysfunction of ALS is clouded by terminology, not only when characterizing the nature of the cognitive impairment or motor deficits, but also in the terminology applied to the neuropathological syndromes. For consistency with the literature, the clinical manifestations of the FTDs are generally held to consist of three syndromes: FTD (predominantly a behavioral disorder), a progressive nonfluent aphasia (PNFA) and semantic dementia.[2] Although any of these can be associated with amyotrophy, few patients with classic ALS will actually meet the full Neary criteria for the diagnosis of a FTD.[3–6] Conversely, when patients with a diagnosis of FTD are examined in detail, a significant proportion will have clinical and electrophysiological features of ALS, suggesting that the true extent of ALS amongst the FTD

population has been under-represented.[7] Although there are instances in which a severe dementia precedes the development of ALS,[8] more commonly ALS patients will manifest with more subtle syndromes of frontotemporal dysfunction either at the onset of symptoms or thereafter.[9] This includes deficits in verbal or design fluency, verbal reasoning, visual attention and problem-solving (ALS with cognitive impairment – ALSci) or deficits in behavioral or executive function (ALS with behavioral impairment – ALSbi) (Table 18.1).[1,10,11] Not all patients with ALS and cognitive impairment will have a FTD, and indeed an overlap with Alzheimer's disease (AD) has been observed (ALS-D), including a frontal predominant variant.[12] FTD can also be associated with a broad range of neuropathological entities, including Pick's disease (PiD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), FTD associated with parkinsonism linked to chromosome 17 (FTDP-17), dementia lacking distinctive histopathology (DLDH), neurofilament inclusion body disease, and FTLD with ubiquitin-only immunoreactive neuronal changes (FTLD-U). The issue here is that the clinical phenotype does not necessarily predict the underlying pathology, as highlighted by the recent report of a progressive akinetic rigid syndrome with supranuclear gaze palsy and cognitive decline consistent with a clinical diagnosis of PSP in which the neuropathology was consistent with either FTLD-U or ALS-FTLD.[13]

On the other hand, there is also considerable overlap amongst the neuropathological descriptors. Typical terminology includes 'FTLD with MND' to refer to those individuals with FTLD and the lesions of ALS, including the presence of ubiquitin-positive, tau-negative and α-synuclein-negative inclusions; 'FTLD-U' to refer to those cases with FTLD and the ubiquitin-only immunoreactive changes (observed amongst individuals with ALS and cognitive impairment) but in whom no evidence of ALS is observed either clinically or neuropathologically. The terminology of 'MND-D' is likely the same entity as 'FTLD with MND' with the inclusion of certain 'core' features (Table 18.2). However, as illustrated by previous authors, a broader repertoire of neuronal inclusions and neuropathological lesions is being recognized amongst the FTLDs, some of which are associated with motor system degeneration and thus this terminology continues in a state of flux.

Table 18.1 Clinical syndromes/terminology

Terminology	*Existing, synonymous terms within the literature*	*Characteristics*
ALS	. . .	A pure motor system disorder as defined by the El Escorial criteria;[10] no clinical evidence of cognitive impairment
ALSci	. . .	Deficits in one or more of verbal and design fluency, verbal reasoning, visual attention, initiation of random movements, and problem-solving, but insufficient to meet the Neary criteria for FTD[1]
ALSbi	. . .	Behavioral or executive dysfunction in association with ALS
ALS-FTD	ALS-dementia (ALS-D), FTD-MND	ALS patient meeting Neary criteria for FTD
FTD-MND-like	. . .	Cases of FTD in which there is neuropathological evidence of motor neuron degeneration, but insufficient to be classified as ALS
ALS-dementia	. . .	ALS with dementia, not typical of FTD

Modified from Lomen-Hoerth and Strong.[11] ALS, amyotrophic lateral sclerosis; ALSci, ALS with cognitive impairment; ALSbi, ALS with behavioral impairment; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; MND, motor neuron disease.

Table 18.2 Core features of FTLD with MND/ALS

- Neuronal loss with spongiform changes in the second and third layers of the frontotemporal cortex
- Neuronal loss in the substantia nigra
- Neuronal loss and astrogliosis in subiculum of the pars hippocampus
- Intraneuronal ubiquitin-positive, tau-negative inclusions in the extramotor cortex
- Motor system pathology consistent with MND/ALS

FTLD, frontotemporal lobe degenerations; MND, motor neuron disease; ALS, amyotrophic lateral sclerosis.

This includes the recently described neuronal intranuclear inclusions observed predominantly in familial FTD-MND cases as well as non-familial variants.[14,15]

To some extent, the problem of overlapping nomenclature of the FTDs can be addressed based on histological features, the characterization of microtubule-associated tau protein expression (predominantly as the insoluble fraction) and on the ubiquitin immunohistochemistry.[16] Using such an approach, FTLDs can be broadly sorted into two categories that include those disorders characterized by tau protein inclusions or those disorders that lack abnormalities in tau. Further classification based upon the nature of inclusions is then applied.[17]

TAU PROTEIN FUNCTION AND METABOLISM

Understanding the nature of microtubule-associated tau protein aggregation, and its molecular characterization, requires an understanding of tau metabolism. In that this has been reviewed in detail elsewhere (see previous chapters), it will only briefly be reviewed here. The primary function of tau protein is to bind to microtubules and to both promote their assembly and enhance their stability in a polymerized state. Hyperphosphorylated tau, as observed in a number of the tauopathies, is a highly insoluble protein that will polymerize in the somatodendritic neuronal compartment and form neurofibrillary tangles. Six alternatively spliced tau isoforms exist in the adult human nervous system, containing either three (3R) or four (4R) microtubule binding domains, with the additional microtubule binding domain encoded by exon 10 (E10) (Fig. 18.1). The aggregation of tau can be directly associated with hyperphosphorylation, or with an alteration in the relative ratio of the 3R and 4R isoforms.

In addition, tau aggregation can also be associated with mutations that can give rise to a number of specific effects on tau metabolism, including impairments in *tau* function, the promotion of tau filament formation, or perturbations in *tau* gene splicing.[18] Mutations in the *tau* gene appear to cause tau protein accumulations by at least two broad mechanisms.[19] In one group, intronic mutations adjacent to the 3′ end of the E10 can lead to an increased expression of the E10 encoded domain, producing a predominance of the 4R tau isoform and thus a greater predominance of the four microtubule binding domain tau isoform. An example of such a mutation is the $^{N}279^{K}$ mutation that strengthens the expression of an exon-splicing enhancer, leading to increased E10 expression. In contrast, the $\Delta 280^{K}$ mutation results in a loss of the exon-splicing enhancer and a loss of E10 expression, leading to a predominance of the 3R tau isoform (with less avid microtubule binding). Within E10 is another regulatory element, the 'exon splicing silencer', which is abolished with the $^{L}284^{L}$ mutation and which thus leads to increased E10 expression. Intronic mutations immediately 5′ adjacent to E10 also appear to result in an increased E10 expression. In the second group of tau mutations, the mutations are associated with abnormalities of tau protein function leading to a reduction in tau affinity and binding to microtubules (e.g. $^{G}272^{V}$, $^{V}337^{M}$, and $^{R}406^{W}$ mutations).

The recognition that different perturbations in tau metabolism can give rise to seemingly unique tau pathology has contributed to the concept that a 'molecular signature' tau neuropathology can be developed for the individual tauopathies. For example, corticobasal degeneration (CBD), a disorder characterized by progressive motor dysfunction with postural abnormalities, can be characterized by the deposition of hyperphosphorylated tau as filamentous inclusions in neurons and glia, with

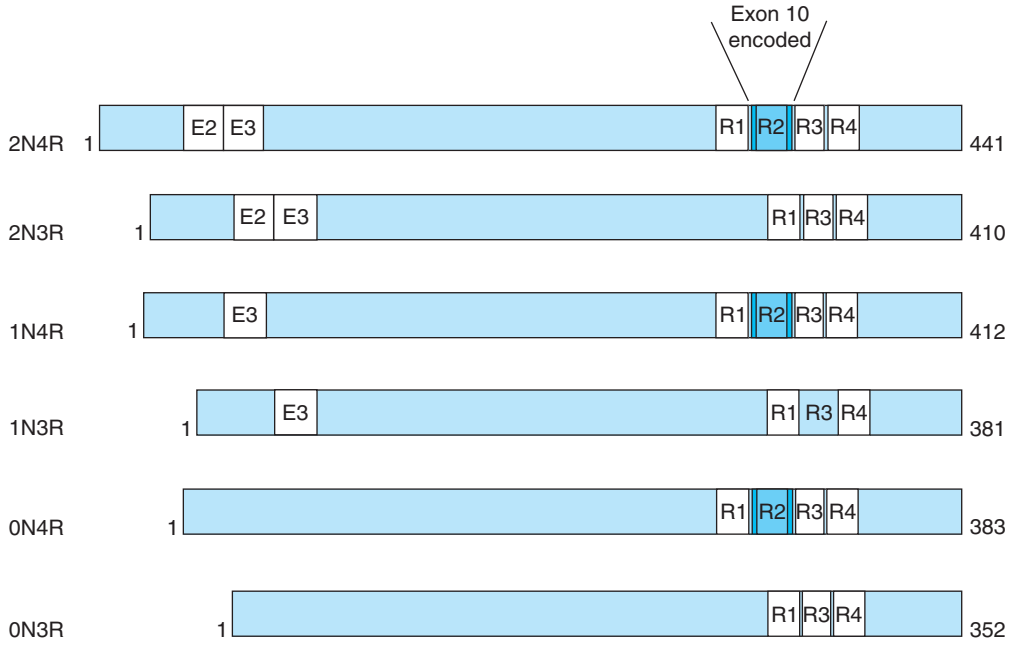

Fig. 18.1 Tau protein: six human tau isoforms are generated by alternative splicing of the *tau* gene which includes 16 exons. Alternative splicing of the E2, E3 and E10 exons produces the six isoforms, with E10 encoding an 18 amino acid microtubule binding repeat. The isoforms range from 352 to 441 amino acids in length.

4R tau as the predominant isoform.[20] The sarkosyl-insoluble tau fraction in both the gray and white matter contained predominantly the hyperphosphorylated 4R tau isoforms, with the isoforms recognized by the monoclonal antibody AT8 (recognizing phosphorylation at Ser-202/Thr-205) specifically increased in the white matter. This is in distinction to Pick's disease, an uncommon FTD marked by prominent frontotemporal degeneration clinically, and neuropathologically by discrete frontal and anterior temporal cortical atrophy with achromatic neurons (Pick cells) and intraneuronal argentophilic inclusions (Pick bodies). The biochemical 'signature' of this tauopathy is the accumulation of both 3R and 4R tau isoforms within both gray and white matter sarkosyl-insoluble fractions.[21] At the level of the immunohistochemical analysis of the intraneuronal aggregates, both CBD and progressive supranuclear palsy (PSP) can be differentiated from Pick's disease by the observation of 4R tau immunostaining of intraneuronal aggregates, a feature not observed in Pick's neuronal aggregates (although observed within glial aggregates).[22] A similar process can be adopted for a number of the remaining tauopathies, including argyrophilic grain disease, dementia lacking distinctive histopathology (DLDH), and AD.[23–26]

ALTERED TAU METABOLISM AND FTD IN ALS

Using the core criteria for a FTLD as presented earlier (Table 18.2), the neuropathological characteristics of either ALS-FTD or ALSci are consistent with a FTLD.[27,28] This includes the presence of spongiform degeneration in frontal and precentral gyrus cortical layers II and III with diffuse subcortical gliosis[4,28–40] and reduced neuronal density in the anterior cingulate gyrus, substantia nigra and amygdala.[41] Microglial proliferation is evident throughout the affected neocortex. Ubiquitin immunoreactive dystrophic neurites are evident in the extramotor cortices, but with a predominance of involvement in the frontal, temporal and hippocampal cortex. Considered by many authors to be the pathological hallmark of ALS-FTD, ubiquitin immunoreactive intraneuronal inclusions are observed within the dentate granule cells, the

superficial frontal and temporal cortical layers, and in the entorhinal cortex. While these inclusions are observed in other forms of neurodegeneration,[40,42-44] in ALS ubiquitin immunoreactive inclusions are unique in not being immunoreactive to either microtubule-associated protein tau or α-synuclein.[35,40,42,43,45,46]

The observation of tau aggregation in sporadic ALS-FTD or ALS-D is more recent. In 1999, Noda and colleagues first described three cases of late adult-onset ALS in which tau immunoreactive thread-like structures were observed in the neuropil and in glial cells (as coiled bodies) in the hippocampus, parahippocampal gyrus and amygdala.[29] In two of the three cases, the neuropil and glial tau immunoreactive structures occurred in the absence of pathology typical of AD. These features can also be seen in cognitively intact ALS patients, although considerably less extensive than observed in cognitively impaired ALS cases.[47] Forno and colleagues observed tau immunoreactive glial inclusions in 10 cases of FTLD in which ubiquitin-positive, tau- and α-synuclein-negative inclusions were found.[48] In one case, clinical evidence of a motor neuron disease was confirmed neuropathologically, while two cases demonstrated neuropathological features suggestive of a motor neuron disease. Martinaud and colleagues have described a family in which ALS and FTD coexisted and in which the neuropathology included widespread tau deposits with the neuropathological features of FTLD.[49] In contrast to the typical findings of ALS-FTD, ubiquitin immunoreactive inclusions in the dentate gyrus were not observed. Tau immunoreactive aggregates were observed in the dentate gyrus, entorhinal cortex, and pyramidal layer of Ammon's horn. Of note, astrocytic plaques, thorn astrocytes and gliosis were not observed, although coiled bodies and threads were observed in the temporal white matter. Using whole tissue homogenates (and thus not fractionating tau on the basis of solubility characteristics), tau immunoblots demonstrated predominantly 64 and 69 kDa isoforms.

The prototypical example of abnormal tau metabolism in ALS remains that of the ALS/parkinsonism-dementia complex of the Western Pacific (see Chapter 14). First reported after World War II in Guam among native Chamorros and termed the amyotrophic lateral sclerosis-parkinsonism dementia complex (ALS-PDC) of Guam,[50,51] approximately 50% of the siblings of these patients developed parkinsonism and dementia, 25% developed ALS, and 5% developed parkinsonism, dementia, and ALS.[52,53] Relevant to this discussion of tau metabolism in ALS, neurofibrillary tangle (NFT) formation morphologically identical to that observed in AD is present.[54–61] In contrast to AD, the hyperphosphorylated, highly insoluble, tau triplet protein (the fundamental constituent of the NFT) is more widely distributed in both cortical and subcortical structures in the western Pacific variant of ALS.[62] Lewy-like bodies, containing accumulations of α-synuclein and typical of those observed in Parkinson's disease, are also observed predominantly within neurons of the amygdala.[63,64] These neuropathological features are similar to those found in patients affected by the ALS-PDC of the Kii peninsula of Japan (Muro disease).[65] In this hyperendemic focus of ALS, bearing many similarities to the ALS/PDC of Guam, the insoluble tau fraction demonstrates a prominent tau triplet of 60, 64 and 68 kDa that resolves to six isoforms following dephosphorylation, similar to that of AD-derived insoluble tau.

The co-occurrence of ALS and FTLD has also been described in families outside Guam as the disinhibition-dementia-parkinsonism-amyotrophy complex.[66,67] In the most extensively studied family (Mo family), personality and behavioral changes consistent with a FTD were the first symptoms in 12 of 13 affected patients.[67] All affected members had rigidity, bradykinesia, and postural instability. The neuropathology was consistent with a FTLD, with two of the affected individuals showing anterior horn cell loss. There were no Lewy bodies, NFTs, or amyloid plaques. This clinical syndrome has been localized to chromosome 17q21-22 and a mutation found in the intron adjacent to exon 10 in the tau gene. Since then, more than 13 families with chromosome 17-linked FTLD have been described.[18,68] Of the 13 families, 4 had corticospinal disturbances, muscle wasting, and fasciculations consistent with a motor neuron

disease. Mutations in the *tau* gene, located on chromosome 17, were found in many of these families, particularly those with extrapyramidal disturbances; however, few FTLD-ALS cases are caused by known tau mutations.[69–72] Subsequently 25 different mutations have been identified in the *tau* gene that are presumed to cause FTLD symptoms.

However, not all chromosome 17-linked pedigrees with ALS and FTD are associated with mutations in the *tau* gene. This includes 'San Francisco family-B' in which several family members had ALS, FTD, or ALS-FTD, and in which linkage to a non-tau locus on chromosome 17 was found.[73] In addition, another FTLD-ALS family in which affected individuals either had ALS, FTLD, or both, has been localized to chromosome 9q21-q22.[74]

At this time, there is no evidence of sporadic ALS with FTD being associated with chromosome 17-linked tau.[75]

ALTERED TAU METABOLISM IN SPORADIC ALSci

We have observed that tau immunoreactive intracellular aggregates are present in both astrocytes and oligodendroglial cells, in addition to those observed in degenerating neurons in ALSci (Fig. 18.2). While the presence of tau immunoreactive neuronal inclusions was not restricted to ALSci cases, being also observed in cognitively intact ALS patients, in ALSci tau immunostaining was more intense and more likely to replace the cytoplasm. The extent of tau aggregation was considerably greater than would be predicted for aging alone.[76] Characteristic of ALSci was the presence of intense tau immunoreactivity within neurons in layers II and III. This latter finding was reminiscent of the distribution of NFTs in Guamanian ALS/PDC.[77] Both the cognitively impaired and cognitively intact ALS cases possessed tau immunoreactive astrocytic inclusions within cortical layer I, deep

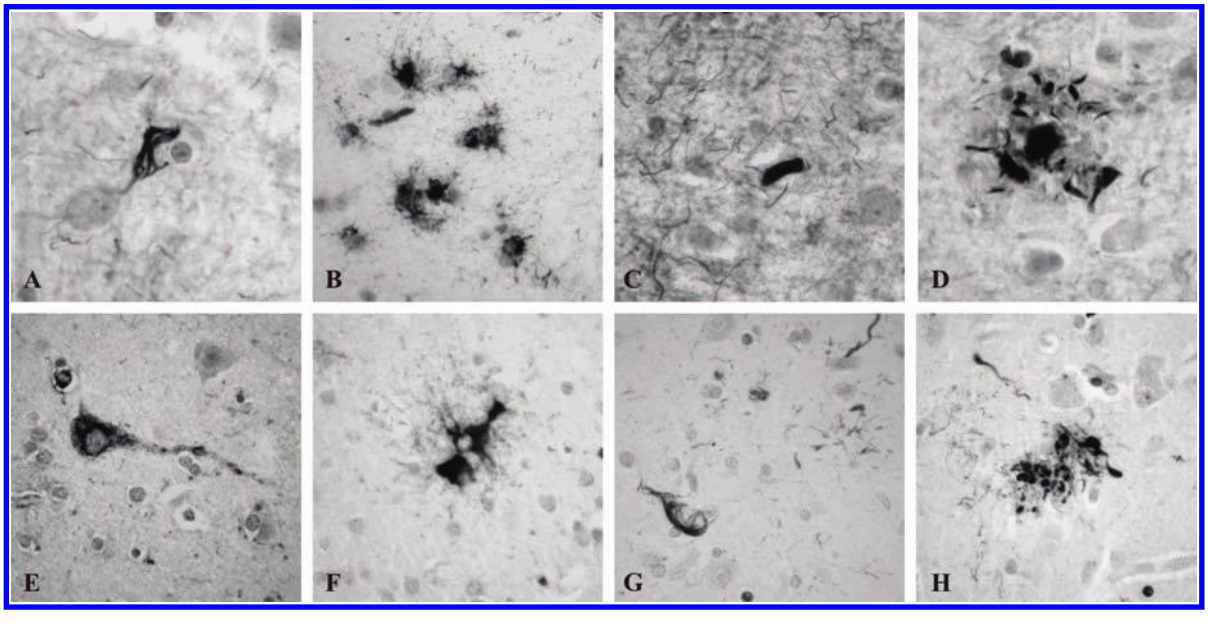

Fig. 18.2 Tau protein aggregation characteristic of frontotemporal lobar degeneration in ALSci. Archival, paraffin-embedded tissue taken at the level of the anterior cingulate gyrus was either stained with the Gallyas-Braak silver stain sensitive to tau aggregation (A–D) or with a mouse monoclonal antibody recognizing phosphorylated tau protein (E–H). Tau aggregation was observed within neurons (A, E), astrocytes (B, F), as extraneuronal neuritic threads (C, G), and as aggregations with the appearance of plaques (D, H). In the latter, no evidence of β-amyloid deposition was found (data not shown) and the density of such plaques was always less than that observed in Alzheimer's disease (magnification before reproduction ×40). Reproduced with permission from Lomen-Hoerth and Strong, 2006.[11]

cortical layers and subcortical white matter. Control cases were free of tau pathology. We also observed astrocytic proliferation, a feature previously described by others.[78–80] In addition to these findings, and unique to the cognitively impaired ALS patients, extraneuronal tau immunoreactive aggregates were observed. These were readily apparent as argentophilic aggregates with Gallyas-Braak silver staining, sensitive to aberrant tau deposition,[81] and assumed a number of morphologies, including curvilinear neuropil threads, rare argyrophilic granules and dense rounded aggregates with irregular fibrillary margins.

When we subsequently purified tau, and differentiated it by solubility characteristics, we observed that both the 3R and 4R tau isoforms were present in the frontal gray and white matter of ALSci patients, including both soluble and insoluble tau isolates, and that tau within the insoluble fraction of ALSci is not the triplet (PHF) tau observed in AD (Fig. 18.3). In contrast to the chromosome 17-linked variants of ALSci, we did not observe tau mutations in sporadic ALSci.[75] Using *E. coli* alkaline phosphatase of tau isolates in solution or bovine alkaline dephosphosphorylation of tau immunoblots, we observed that tau isolated from ALSci was phosphatase-resistant. When soluble tau isolated from ALSci frontal cortex was purified and subjected to LC/MS/MS, we found novel tau phosphoepitopes (Thr175, Ser208, Ser210, Ser237).[82]

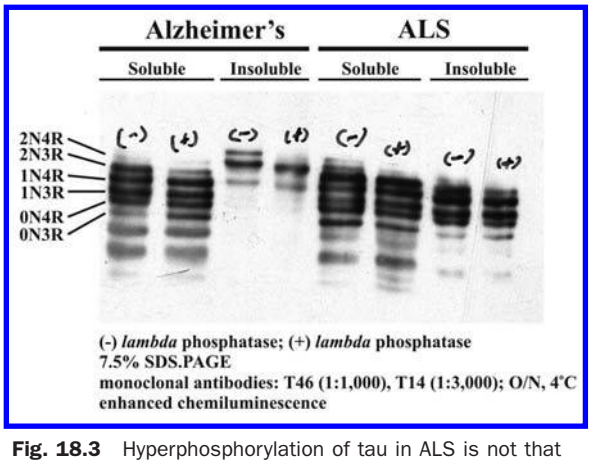

Fig. 18.3 Hyperphosphorylation of tau in ALS is not that observed in Alzheimer's disease (AD). Tau protein was isolated from both ALS and AD and separated into both soluble and insoluble fractions prior to dephosphorylation with lambda alkaline phosphatase. The typical PHF triplet protein is observed in the AD-insoluble fraction compared to the expression of the full complement of tau isoforms in the ALS case.

Taken together, these findings suggest that in a population of ALS patients, selected on the basis of cognitive impairment ante mortem, alterations in tau metabolism are evident in the presence of otherwise typical features of a FTLD. The observation of tau hyperphosphorylation, intact expression of both the 3R and 4R isoforms, and the failure to find chromosome 17-linked tau mutations, all suggest that a post-translation modification in tau phosphorylation state can be associated with ALS.

CONCLUSIONS

To date, the clinical, neuropathological, neurochemical and genetic studies suggest that the occurrence of FTD or FTLD in ALS consists of a heterogeneous spectrum of disorders. Clinically, FTD in ALS can be expressed as either a full FTD meeting the Neary criteria for diagnosis, or more subtle syndromes consisting of predominantly cognitive, behavioral or executive dysfunction. The neuropathological spectrum can consist of the core features of FTLD, with or without the presence of ubiquitin-positive, tau- and α-synuclein-negative intraneuronal inclusions in the dentate gyrus. However, it is also increasingly evident that a range of tau immunoreactive neuronal and extraneuronal aggregates can be observed, and that this pathology includes hyperendemic variants of ALS in Guam and the Kii Peninsula, familial variants of FTD with ALS in the presence or absence of linkage to either chromosome 9 or 17, and at least some cases of sporadic ALSci and ALS-FTD. In the latter variants, tau can be characterized as being hyperphosphorylated and thus, for at least a subpopulation of ALS patients, there is evidence for an associated tauopathy (Fig. 18.4). It is too early in our understanding of this spectrum for dogmatic classifications which define ALS-FTD, ALSci or ALSbi as disorders with or without alterations in tau metabolism and indeed, until such time as careful clinicopathological

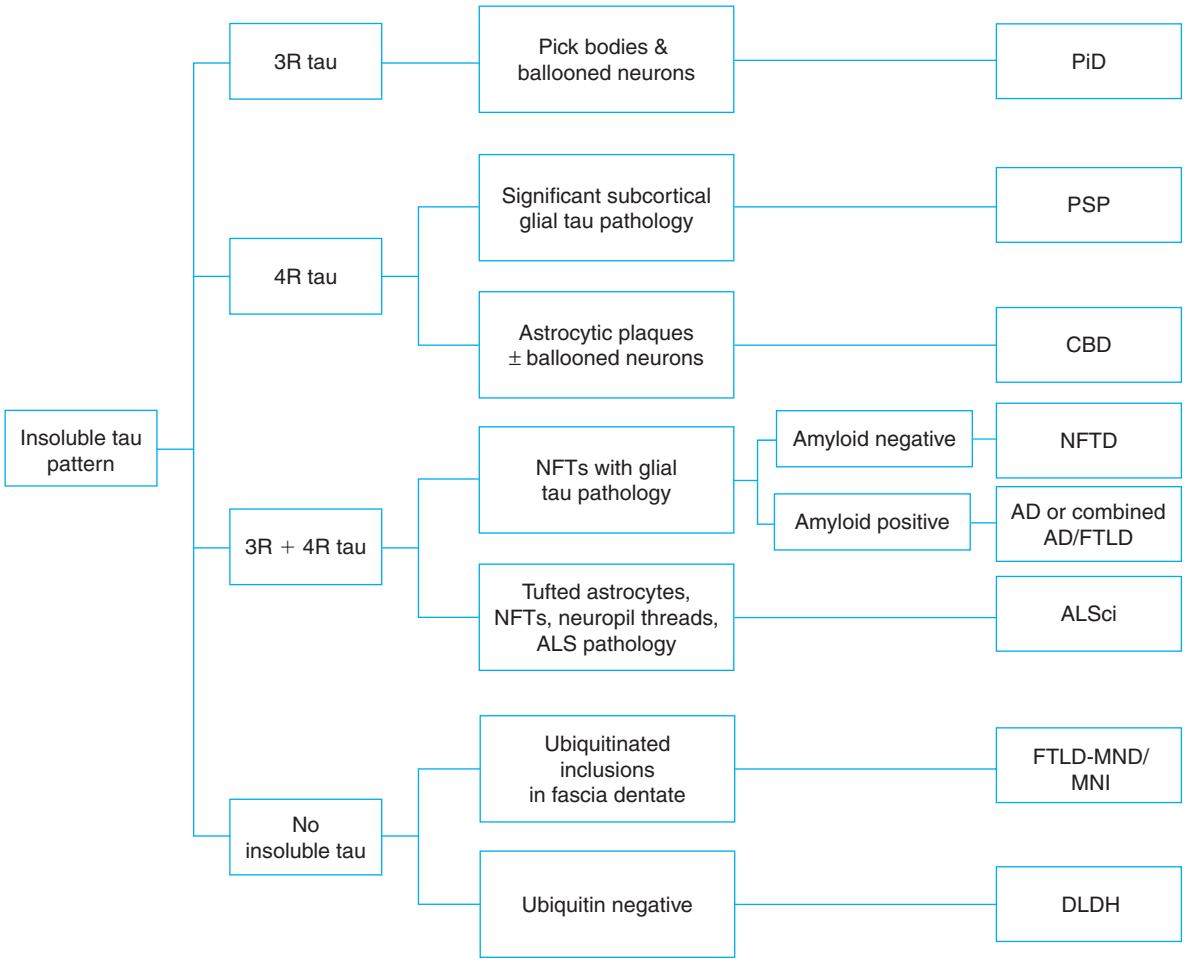

Fig. 18.4 A diagnostic algorithm for the frontotemporal dementias (modified from Mott et al.[17]). In this algorithm, FTLDs are separated firstly on the basis of the nature of tau isoforms observed in the sarkosyl-insoluble fraction, initially in terms of the presence or absence of insoluble tau protein, and then the nature of the 3R or 4R tau isoform expression. In this modification, the evidence that certain forms of ALS with FTD are associated with the presence of insoluble 3R and 4R isoforms of tau is considered and that this is associated with tau immunoreactive intraneuronal inclusions, tufted astrocytes and neuropil threads. AD, Alzheimer's disease; ALSci, ALS with cognitive impairment; CBD, corticobasal degeneration; DLDH, dementia lacking distinctive histopathology; NFT, neurofibrillary tangles; NFTD, neurofibrillary tangle dementia; PiD, Pick's disease; PSP, progressive supranuclear palsy.

correlative studies are undertaken in which ALS patients are carefully characterized with regards to cognitive status ante mortem, such statements cannot be validated.

The likelihood is, however, that the frontotemporal syndromes of ALS will encompass a heterogeneous clinicopathological syndrome with various neuropathologies superimposed on the more traditional pathology of ALS. Amongst this grouping will be those disorders in which ALS coexists with alterations in tau metabolism.

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Frontotemporal syndromes in the motor neuron diseases

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INTRODUCTION

From its first clinical description, amyotrophic lateral sclerosis (ALS) has been traditionally considered to be the prototypic single systems disorder, reflective of a progressive degeneration of the motor system. However, as highlighted in this volume, the observation of sporadic cases of dementia or cognitive impairment with progressive amyotrophy, with or without pathologically brisk reflexes, has given rise to the broader realization that alterations in frontotemporal function are indeed common in ALS. This has led to the contemporary conceptualization that, while ALS is predominantly a disorder of the motor neurons, it is in fact a multisystems disorder in which the involvement of the motor system is one of selectivity and not necessarily specificity.

Defining ALS on the basis of both motor and cognitive deficits is not a trivial point. As highlighted by Murphy and colleagues (Chapter 5), survival time is shorter in ALS patients with a frontotemporal dysfunction syndrome, perhaps due to the lack of compliance or interest in invasive therapies such as enteral nutrition or in the use of noninvasive positive pressure ventilation.[1] Compared with individuals afflicted with Alzheimer's disease, overall survival amongst those affected with frontotemporal lobar degeneration (FTLD) is shorter – a phenomenon that is most marked in those patients with FTLD coexistent with motor neuron disease.[2,3]

The observation of frontotemporal lobar dysfunction in ALS patients is also of considerable biological interest in that there appears to be a spectrum of clinical deficits in ALS patients that may be suggestive of neuroanatomic regional variability in the disease process. In a proportion of cases, including the western Pacific variants and a number of sporadic forms of ALS, microtubule-associated tau protein (tau) immunoreactive neuronal and non-neuronal cells are observed in addition to the more typical feature of ubiquitin-positive, tau- and α-synuclein-negative neuronal inclusions.[4–6] This suggests, at some level, a commonality of ALS with other degenerative disease states in which FTLD is the primary neuropathological finding. This postulate is highlighted by the finding of ubiquitin immunoreactive intraneuronal aggregates within both bulbar and spinal motor neurons in a population of FTLD autopsies in which there is no obvious ante-mortem evidence of a motor neuron disease.[7,8]

In this text, we have examined the clinical, anatomic and neuropathological basis upon which the non-motor system involvement of ALS is reflected in cognitive impairment. The focus of this concluding chapter is to place these observations into context.

TERMINOLOGY: THE NEED FOR CLARITY

There is no consistent view to the terminology applied to the cognitive and behavioral impairment that can occur in ALS, and indeed, the concept of cognitive and behavioral impairment has in fact been driven by three populations of special interest: the neuropsychologist whose primary interest is in disorders of cognition and dementia; the neurologist whose primary interest is in the motor system disorders of aging; and the neuropathologist whose primary interest is in clinicoanatomic correlates. While none of these vantages is wrong, this has led to an intersection of terminologies applied to the frontotemporal syndromes associated with ALS in which pathological processes have been implied in the absence of overt evidence of such pathology, or conversely, terminologies in which a clinical manifestation is implied based on neuropathological findings. For example, the neuropathological term 'FTD-MND-like', while of inherent neuropathological accuracy, is meaningless from a clinical point of view and of no clinical utility in patient categorization ante mortem. However, the recognition that significant overlap exists amongst the frontotemporal dementias (FTDs), the motor system degenerative diseases, and the multisystem disorders, is of utility.

Defining ALS – internationally accepted criteria

This problem becomes increasingly complex when one begins to consider a minimum diagnostic algorithm required to classify individuals presenting with a motor system disorder. While there is some confusion with regards to the nomenclature of the nonmotor cognitive and behavioral manifestations of ALS, there is clarity with regards to internationally accepted criteria for the diagnosis of ALS. In their revised format, these criteria make use of clinical, electrophysiological, genetic and to some extent neuroimaging modalities to apply a level of certainty to the diagnosis of ALS.[9,10] When describing the motor neuron degenerative disease that is associated with cognitive and behavioral impairment, these criteria should be at the core.

Using these internationally accepted criteria (El Escorial criteria), ALS can be defined as clinically definite, probable, possible or suspected. In essence, the diagnosis of ALS requires the presence of lower motor neuron (LMN) degeneration (by clinical, electrophysiological or neuropathological criteria), evidence of upper motor neuron (UMN) degeneration (by clinical exam) with evidence of progression of symptoms or signs within a region or to other regions. These features must be present in the absence of electrophysiological or pathological evidence of alternate disease processes that would explain the signs, or neuroimaging evidence of other disease processes that would explain the observed clinical or electrophysiological signs. Ross et al. subsequently simplified these criteria (Table 19.1).[11] In a subsequent revision of the El Escorial criteria, laboratory and genetically supported categories were added to recognize those individuals in whom the full clinical and electrophysiological criteria are not met.[10]

Table 19.1 A diagnostic algorithm

Exclude disorders known to mimic ALS

Diagnosis of ALS is tenured if:
- Lower motor neuron signs in at least two regions
- Upper motor neuron signs in at least one region
- Progression

Absence of:
- Sensory signs
- Neurogenic sphincter abnormalities
- Clinically evident peripheral nervous system disease with natural history of progression, distinct from ALS
- Clinically evident peripheral nervous system disease with a natural history of progression
- ALS-like syndromes

Modified from Ross et al.[11]

- **Clinically definite ALS**: defined on clinical evidence alone by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions, or the presence of UMN and LMN signs in at least three spinal regions.
- **Clinically probable ALS**: defined on clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to the LMN signs.
- **Clinically probable ALS – laboratory supported**: defined when clinical signs of UMN and LMN dysfunction alone are present in one region, and LMN signs defined by EMG criteria are present in at least two regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.
- **Clinically possible ALS:** defined when clinical signs of UMN and LMN dysfunction are found together in only one region, or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of clinically probable ALS – laboratory supported cannot be proven.
- **Clinically suspected ALS**: where the diagnosis could not be regarded as sufficiently certain to include the patient in a research study.

In those families in which a genetic linkage is known, the term '**clinically definite familial ALS – laboratory supported**' may be applied when ALS presents with progressive UMN and/or LMN signs in at least one region (in the absence of another cause for the abnormal neurological signs).

While these criteria were initially developed with a view towards enhancing the diagnostic accuracy and rate of enrollment of individuals with ALS into clinical trials, the criteria have taken on added significance when one now considers the nonmotor syndromes that may occur in ALS, and the need to ensure that ALS remains the core aspect of the diagnosis. Although not studied in a fashion that speaks to the co-existence of ALS and a frontotemporal lobar syndrome, the sensitivity and specificity of the El Escorial criteria as diagnostic criteria for ALS have been validated in neuropathological studies.[12]

Frontotemporal lobar syndromes in ALS

Although our understanding of the nature of the nonmotor syndromes that can occur in ALS remains in its infancy, there are several key points on which there is some degree of consensus. The most common manifestation is that of a frontotemporal lobar syndrome, with florid dementia in fact being uncommon, although as discussed by Tanaka and Okamoto (Chapter 7) and Katsuse and colleagues (Chapter 15), the more florid dementia preceding ALS that has been described amongst the Japanese population can be included in this categorization. A frontally predominant variant of Alzheimer's disease can also occur in ALS, although it is not clear whether this is a chance association.[13]

For consistency within the literature, it is reasonable to consider the frontotemporal lobar syndromes that may occur in ALS as residing within the rubric of frontotemporal lobar degeneration (FTLD), the over-arching term representing the neuropathological basis of three well-defined syndromes.[14] Under the rubric of FTLD, the most common is a progressive behavioral syndrome, i.e. frontotemporal dementia (FTD), marked predominantly by a loss of insight, decline in interpersonal conduct, emotional blunting and impaired regulation of personal conduct. In addition to this syndrome, FTLD produces progressive nonfluent aphasia and semantic dementia (related to deficits in expressive language and semantic knowledge, respectively).

Whereas the classification of patients with FTLD into FTD, progressive nonfluent aphasia and semantic dementia has in general proven very useful, this approach may not serve to adequately describe the spectrum of cognitive and behavioral syndromes associated with ALS. For example, a frontal dysexecutive syndrome may occur in ALS in the absence of the typical behavioral features associated with FTD based on the Neary criteria. As highlighted within the text, these nuances of neuropsychological differences between ALS and FTLD may in fact relate

to significant differences in not only neuroanatomic substrate, but neurochemical deficits. None of the standard criteria for FTD speak directly to the issue of executive dysfunction in ALS, deficits of which may impact directly on the ability to organize information mentally, to shift attention, or inhibit behavior. Although each of these entities alone has been considered uncommon in ALS, detailed neuropsychological testing, using paradigms sensitive to frontotemporal lobar dysfunction, suggests that their prevalence in the ALS population may approach 50%.[15] Further, it is not clear that the cognitive and behavioral syndromes in ALS can be viewed as discrete entities as opposed to a continuum of disease.

The issue then becomes defining a minimum set of criteria that will be both sensitive and specific to these various syndromes. It is worth emphasizing again that the neuropsychological impairments observed in ALS are subtle for the vast majority, with the commonly observed deficits in the areas of problem-solving, attention/mental control, continuous visual recognition memory, word generation, and verbal free recall (see Chapters 8 and 11). Furthermore, the interpretation of deficits can potentially be confounded by numerous extraneous variables, and thus there is a need to identify and control for such variables when evaluating a patient with ALS with respect to cognitive dysfunction (Table 19.2). While sampling the major cognitive domains, neuropsychological assessments should include tests weighted towards executive functioning, including a verbal fluency measure, as well as a caregiver interview measuring emotional and behavioral functioning. The latter is critical in that many reported series assessing frontotemporal lobar function in ALS have not addressed the behavioral aspects, but rather have focused on alterations in cognition. A further challenge in assessing individuals with ALS is to choose tests which minimize the impact of speech and motor dysfunction. To date, a variety of testing measures have been successfully employed with the ALS population, but there would be utility in developing a consensus of specific measures to use. Finally, all patients should be evaluated with regards to whether they meet the Neary criteria for FTD.[14] Applying an evaluative approach such as this will allow for a crisper categorization of the frontotemporal lobar syndromes in ALS (Table 19.3). While the development of a brief screening tool for a frontotemporal lobar syndrome in ALS would be a highly valued clinical tool for those clinics and researchers for whom a full neuropsychological assessment is not available, such a tool has not yet been validated in this population.

Table 19.2 Extraneous variables to consider in the neuropsychological evaluation of ALS

- Depression
- Pseudobulbar affect
- Educational level/baseline intellectual functioning
- Presence of bulbar dysfunction (e.g. dysarthria)
- Level of disease progression
- Pulmonary status
- Pain
- Fatigue
- Medications (especially psychotrophic and analgesic medications)
- Level of motor impairment

NEUROIMAGING STUDIES

Although neuroimaging plays a critical role in defining the regions of pathological interest in the nonmotor manifestations of ALS, it is less clear that these tools are yet robust enough to be utilized as diagnostic tools in the evaluation paradigm for cognitive dysfunction in ALS. However, as discussed by Pioro (Chapter 10), imaging modalities sensitive to frontal atrophy can be used, as can tests sensitive to neuronal loss or metabolic dysfunction. It would seem that the presence of frontotemporal atrophy, whether defined by CT scan or MR imaging, may be a sensitive early indicator of a FTLD in ALS. There is only a single study using MR spectroscopy to define the extent of neuronal loss in the anterior cingulate gyrus as a function of disease progression in ALS, and thus it is not yet clear that this modality can be utilized in a more robust fashion.[16] More dynamic tests of metabolic function, cerebral perfusion,

Table 19.3 Diagnostic classification for ALS cognitive and behavioral dysfunction

Heading	*Subheadings*	*Existing, synonymous terms within the literature*	*Characteristics*
ALS	ALS		A pure motor system disorder as defined by the El Escorial criteria; no clinical evidence of frontotemporal dysfunction
Frontotemporal lobar degeneration with ALS			
	ALSci		Deficits in frontal cognitive function but insufficient to meet the Neary criteria for FTD
	ALSbi		Behavioral dysfunction but insufficient to meet the Neary criteria
	ALS-FTD	ALS-dementia (ALS-D), FTD-MND	ALS patient meeting Neary criteria for FTD
	ALS-PA		ALS patient meeting Neary criteria for PA
	ALS-SD		ALS patient meeting Neary criteria for SD
	FTD-MND-like		Cases of FTLD in which there is neuropathological evidence of motor neuron degeneration, but insufficient to be classified as ALS
	ALS-dementia		ALS with dementia, not typical of FTLD
	ALS-parkinsonism-dementia complex	Western Pacific variant of ALS; lytico bodig	ALS concurrent with dementia and/or parkinsonism occurring in hyperendemic foci of the western Pacific

astrocytic proliferation, or microglial activation remain investigative tools at this time but do show significant promise (as highlighted in Chapter 11).

MOLECULAR AND GENETIC DIAGNOSIS

It is difficult to know where to place the western Pacific variant of ALS amongst these disorders, and indeed as suggested by Perl (Chapter 14) it may well be the prototypic disorder in which nonmotor manifestations of ALS can be analyzed. First reported after World War II in Guam among native Chamorros and termed the amyotrophic lateral sclerosis-parkinsonism dementia complex of Guam,[17,18] approximately 50% of the siblings of these patients develop parkinsonism and dementia, 25% develop ALS, and 5% of the siblings develop parkinsonism, dementia, and ALS.[19,20]

Of relevance to this discussion, the co-occurrence of ALS and FTLD have also been described in families outside Guam as the dis-inhibition-dementia-parkinsonism-amyotrophy complex.[21,22] In the most extensively studied family (Mo family), personality and behavioral changes were the first symptoms in 12 of 13 affected patients.[22] Symptom onset was around age 45 on average and the mean duration to death was 13 years. There was early memory loss, anomia, and poor construction with later involvement of orientation, speech, and calculations. All affected members had rigidity, bradykinesia, and postural instability. On neuropathology, there was atrophy and spongiform change in the frontotemporal cortex, and neuronal loss and gliosis in the substantia nigra and amygdala. Two individuals had anterior horn cell loss and one subject had fasciculations and muscle wasting. There were no Lewy bodies, neurofibrillary tangles, or amyloid plaques. The genetic locus was linked to chromosome 17q21-22 and a mutation found in the intron adjacent to exon 10 in the *tau* gene.

An extensive number of kindreds with FTLD and linkage to chromosome 17 has been

described.[23,24] In a small proportion of these patients, corticospinal disturbances, muscle wasting, and fasciculations are observed. Mutations in the *tau* gene, located on chromosome 17, are found in many of these families, particularly those with extrapyramidal disturbances; however, few FTLD-ALS cases are caused by known tau mutations.[25–28] The relationship between chromosome 17 linkage and FTLD is complex, and while over 25 different mutations have been identified in the *tau* gene (localized to chromosome 17) that are presumed to cause FTLD symptoms, non-tau-linked chromosome 17-linked FTLD with ALS is evident.[29] In addition, another FTLD-ALS family has been localized to chromosome 9q21-q22.[30]

NEUROPATHOLOGICAL CORRELATES

The neuropathological characterization of the FTLD associated with ALS remains to be fully clarified. If we continue with the thread that the basis of the clinical syndrome remains ALS, then the neuropathological characterization thereafter follows. In short, the neuropathological classification of FTLD as ALS-FTLD or FTLD-MND in the absence of overt clinical evidence of ALS, or classically defined neuropathological features of ALS, should not occur. The problem then becomes the classification of those patients in whom there is no ante-mortem evidence of ALS, but in whom the features of FTLD are found concurrently with one or more aspects of the neuropathology of ALS.

Neuropathology of ALS

As with the clinical criteria for the diagnosis of ALS, there are minimum criteria for the neuropathological diagnosis of ALS.[9] There must be evidence of motor system degeneration that includes the loss of anterior horn cells (AHC), brainstem motor nuclei, and the descending supraspinal pathways involved in motor function. This degenerative process is accompanied by a wide array of neuropathological features in which both cortical (UMN) and either brainstem motor neurons or AHC (LMN) are involved. Amongst the neuropathological hallmarks of ALS are a variety of intracellular inclusions, including Bunina bodies, ubiquitinated inclusions or skein-like structures, and hyaline conglomerates.[31–36] Although none of these findings are pathognomonic, many are sufficiently unique to ALS (as discussed by Brockington and colleagues, Chapter 4) to render the diagnosis of ALS highly likely.

Neuropathology of ALSci

The full extent of the neuropathological basis of the frontotemporal dysfunction syndromes of ALS remains to be defined, and will of necessity require detailed clinicopathological studies. For those individuals with ALSci, the neuropathological features are typical of FTLD,[4,6] including spongiform degeneration in frontal and precentral gyrus cortical layers II and III with diffuse subcortical gliosis.[6,14,37–48] There is neuronal loss in the anterior cingulate gyrus, substantia nigra and amygdala.[49] The finding of microglial activation and proliferation throughout the affected neocortex is reminiscent of the PET imaging studies using markers of microglial activation.

The neuropathological hallmark of FTLD in ALS is the presence of ubiquitin immunoreactive intraneuronal inclusions within the dentate granule cells, the superficial frontal and temporal cortical layers, and the entorhinal cortex. It is critical to note, however, that these are not specific to cognitively impaired ALS cases and can be observed in other forms of neurodegeneration.[48,50–52] It is the fact that these ubiquitin immunoreactive inclusions lack immunoreactivity to either microtubule-associated protein tau or α-synuclein that has led to their being considered unique to ALS.[43,48,50,51,53,54] In addition to these findings, ubiquitin immunoreactive dystrophic neurites in the extramotor cortices with a predominance of involvement in the frontal, temporal and hippocampal cortex are also observed.

FTLD with ALS-like pathology

There then remains a group of FTLDs in which motor neuron degeneration is observed at neuropathological examination. The FTLDs, as discussed by Cairns and Bigio (Chapters 12 and

13) are a heterogeneous group of diseases, sharing in common features of FTLD, but in which there is also considerable overlap in neuropathological features. In addition to this, the classification of the FTDs is a work in evolution, modified by newer neurochemical studies, and by newer immunohistochemical markers.[55] To highlight this, in a recent analysis of 29 cases derived from a brain bank which had been previously classified neuropathologically as FTD, the majority of cases were non-tauopathies, with the most common diagnosis that of FTLD with ubiquitin-only immunoreactive neuronal changes.[56] Other diagnoses included Pick's disease, FTD with parkinsonism linked to chromosome 17 (FTDP-17), FTLD (also known as dementia lacking distinctive histopathology – DLDH), FTLD with motor neuron disease (FTLD-MND), and neurofilament inclusion body disease (NIBD).

The finding of motor neuron ubiquitin immunoreactive aggregates in the presence of the pathological features of a FTD but in the absence of overt clinical features of motor neuron disease has led to the concept of a unique FTD termed 'motor neuron disease inclusion dementia' (MNDID).[7] Of interest has been the observation of ubiquitinated intranuclear inclusions (Ub-INI) in the striatum of patients with familial MNDID only. Ub-INI had previously been described in nine cases of MNDID, none of which had ALS.[8] Of these, one has subsequently developed ALS. It is not clear whether this is the same entity as described by MacKenzie and Feldman (2004) in which intranuclear ubiquitin immunoreactive inclusions were observed in the majority of familial FTD-MND-like cases.[57] However, it is likely that these inclusions can be seen in both ALS-D and FTDs with motor neuron degeneration not typical of ALS (referred to as FTD-MND-like).[58]

A conceptually important and novel entity is the recent description of FTD with neurofilament inclusion bodies (NIBD). The index case demonstrated features of florid FTD, both clinical and neuropathologically, with motor neuron disease, with tau-negative, neurofilament immunoreactive inclusions.[59] Although some of the inclusions had the morphology of Pick bodies, they were not immunoreactive to PHF-1 immunostaining. Unfortunately, the autopsy was limited to the brain only and hence the extent to which this overlaps with ALS or ALS-D remains uncertain. It is likely however, based on the observation of anterior horn neuronal loss with neurophagia in the upper cervical cord that was available for examination, that this was indeed a cross-over case of FTD with ALS in which neurofilament aggregates outside the motor neurons were evident.

SUMMARY

Increasingly, the nonmotor, cognitive manifestations of ALS can be considered reflective of a heterogeneous group of 'frontotemporal dysfunction syndromes' that include cognitive dysfunction (including a dysexecutive syndrome), behavioral impairment, and in a proportion, a florid FTD consistent with the Neary criteria. However, the impairments in the vast majority of these syndromes are relatively subtle and are not characteristic of a fulminant dementia. Consequently, cognitive and behavioral features are often overlooked in a neurological exam of a severely dysarthric and/or severely weak individual, even amongst those attuned to their potential existence. Day to day variability in decision making, impulsivity and emotional lability are less critically inventoried in an individual in whom the devastating nature of the illness mandates a broadly based multisystem and multidisciplinary approach to management. The administration of a detailed neuropsychological examination to detect the nuances of a dysexecutive syndrome exceeds the resources of the majority of clinics. However, in careful studies of cognitive function in ALS, such phenomena are frequent, suggesting that the conceptualization of ALS as a pure motor system disorder needs a radical overhaul.

There is some urgency to resolving these issues. If the frontotemporal lobar syndromes of ALS are simply intersecting diseases, independent in their biology from 'pure' ALS, then defining what is 'pure' ALS becomes critical to future therapeutic trials in ALS.[60] If however a frontotemporal lobar syndrome, and its attendant biological processes, is an integral component of ALS and related motor neuron disorders, then

our research focus needs to dramatically shift from understanding a motor system-specific disorder, to one in which motor neurons are but the 'singing canaries' of the demise of the nervous system. Either way, the recognition and acceptance of the presence of a frontotemporal degenerative state in the context of ALS heralds a new direction in our understanding of this disorder.

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