

ORIGINAL ARTICLE

A Familial Form of Pallidolusio-nigral Degeneration and Amyotrophic Lateral Sclerosis With Divergent Clinical Presentations

Carlos Portera-Cailliau, MD, PhD, Carsten Russ,* PhD, Robert H. Brown, Jr., DPhil, MD, Andrew E. Budson, MD, Jean-Paul Vonsattel, MD, Rebecca D. Folkerth, MD, and Joseph C. Corbo, MD, PhD

Abstract

We describe a family with a rapidly progressive neurodegenerative disorder characterized by amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) but with unusual neuropathologic features that include pallidolusio-nigral degeneration. The proband presented with primary progressive aphasia that evolved into mutism. He subsequently developed dementia with mild disinhibition and parkinsonism and late in the disease showed evidence of motor neuron disease. Two other cases (the proband's mother and maternal uncle) had features of ALS exclusively. All 3 had a young onset (fourth decade) and rapid clinical course, with average time from onset of symptoms to death of 4 years. Postmortem neuropathologic examination of the proband and his uncle showed ALS changes and extensive pallidolusio-nigral degeneration without neurofibrillary tangles, ubiquitin inclusions, or detectable abnormalities in the dentate nucleus of the cerebellum. Although this exceptional combination of neuropathologic features has been described in rare cases of sporadic ALS-FTD, no pedigrees have ever been reported. In 2 affected members of this family, we failed to identify mutations in genes associated with weakness, movement disorders, or dementia, including ALS, FTD, selected spinocerebellar ataxias, and Huntington disease. Thus, this

disorder may represent a novel autosomal dominantly inherited and rapidly progressive neurodegenerative disorder with a spectrum of clinical presentations but common neuropathologic features.

Key Words: ALS-FTD, Frontotemporal dementia, Motor neuron disease, Parkinsonism, Primary progressive aphasia, Tau, Ubiquitin.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive disease that results from degeneration of both upper and lower motor neurons. In a minority of patients with ALS, motor neuron disease is part of a multisystem neurodegenerative disorder that includes frontotemporal dementia (FTD), primary progressive aphasia, and/or parkinsonism (1–3). Interestingly, up to 50% of patients with ALS without dementia have some disturbance of executive functions (4, 5), and as many as one third of patients with FTD have subclinical evidence of motor neuron disease, as assessed by electromyography (6). This finding suggests that there exists a group of disorders along an ALS-FTD spectrum that share common pathophysiologic mechanisms, but that are triggered by distinct gene-environment interactions.

There are also several reports of ALS-FTD kindreds, and specific genetic defects are beginning to be identified in those families (7). Recent analyses of pedigrees with cosegregation of ALS and FTD have identified mutations in the genes *CHMP2B* (8), *DCNI* (9) and *PGRN* (10). There also appears to be a major disease locus for ALS-FTD on chromosome 9p21 (11–13) and another on chromosome 17 (not *MAPT*) (14, 15). Older reports of linkage to 9q21–22 (16) have not yet led to the identification of specific gene mutations (7). In most other pedigrees, including a Swedish pedigree (17) and a Dutch pedigree with juvenile ALS-FTD (18), genetic linkage has not been established. Within all of these families, ALS and FTD can occur concurrently within the same individual, although this is not always the case (13). In addition to familial ALS-FTD, there are several descriptions of sporadic ALS cases arising concurrently with FTD (6, 14, 15, 19).

Clinically, it is sometimes challenging to distinguish ALS-FTD from other neurodegenerative disorders with

From the Departments of Neurology (CPC), University of California Los Angeles, Los Angeles, California; Department of Neurology (CR, RHB), Massachusetts General Hospital, Boston, Massachusetts; Cecil B. Day Laboratory for Neuromuscular Research (RHB), Massachusetts General Hospital, Charlestown, Massachusetts; Departments of Neurology (AEB) and Pathology (RDF), Brigham and Women's Hospital, Boston, Massachusetts; Department of Pathology (JPV), Columbia University Medical Center, New York, New York; and Department of Pathology and Immunology (RCC), Washington University School of Medicine, St. Louis, Missouri.

*Current address: The Broad Institute of MIT and Harvard, Cambridge, Massachusetts.

Send correspondence and reprint requests to: Carlos Portera-Cailliau, MD, PhD, UCLA Department of Neurology, Reed Neurological Research Center, A-145, 710 Westwood Plaza, Los Angeles, CA 90095; E-mail: cpcailiau@mednet.ucla.edu

This work was supported by awards to RHB from the Angel Fund, the National Institutes of Health (National Institute on Aging and National Institute of Neurological Disorders and Stroke), the ALS Association, the Al-Athel ALS Research Foundation, Project ALS, and the Pierre de Bourgnicht ALS Research Foundation.

dementia. In ALS-FTD there are early manifestations of frontal degeneration, including disinhibition and loss of organizational and executive skills, with relative preservation of memory. Another early symptom in ALS-FTD patients can be difficulty initiating speech, leading to mutism, sometimes referred to as “aphasic dementia” with motor neuron disease (20). Manifestations related to basal ganglia dysfunction (e.g. parkinsonism) are unusual. Neuroimaging shows atrophy of the frontal and temporal lobes. Mean age of onset is in the fifth or sixth decade of life (21). FTD progresses to death faster than Alzheimer disease, with a median survival of 8.7 years from onset (22), but some cases are fulminant with a time course typical of ALS (23–25).

The early disinhibition and personality change, language deficits, and apathy are reminiscent of FTD patients without motor neuron disease (26). The preponderance of pyramidal, lower motor neuron, and frontal involvement in typical ALS-FTD distinguishes this entity from the “disinhibition-dementia-parkinsonism-amyotrophy complex” (21). In the latter, there is often a long-standing history of peculiar behavior, which is sometimes described as schizophreniform, and there may also be prominent parkinsonian features. Another differential diagnostic consideration in the initial stages is Pick disease, which demonstrates striking frontotemporal features but lacks the motor component (27).

The classic neuropathologic features associated with ALS-FTD include the following: 1) macroscopic atrophy, most prominent in the frontotemporal regions, with secondary ventricular enlargement; 2) loss of motor neurons in the spinal cord and motor cortex; 3) neuronal cell loss with astrogliosis in frontal lobes and within the medial cortex of

the rostral temporal lobe and in the CA1-subiculum region of the hippocampus (28); 4) microvacuolar degeneration of the superficial layers of cortex and possible involvement of the hippocampus, parahippocampal gyrus, and amygdaloid nuclei (29–31); and 5) ubiquitin-positive cytoplasmic, neuronal inclusions (32). Of note, by contrast with several other degenerative disorders, some pathologic findings in ALS-FTD are not increased beyond levels expected for age, including tau-positive intraneuronal tangles, neuritic plaques, Pick bodies, or Lewy bodies (31, 33).

In addition to ALS-FTD, there are several reports that describe sporadic cases of ALS with multisystem degeneration, most typically involving the pallidum, substantia nigra, and subthalamic nucleus (34–41). These isolated cases show a wide range of illness duration and age at the time of death.

Here we describe a novel familial and rapidly progressive neurodegenerative disorder that presented with symptoms of FTD followed by ALS in the proband and ALS alone in 2 affected relatives. Strikingly, neuropathologic analysis of 2 members of this pedigree show typical ALS findings with marked pallidoluysionigral degeneration (PLND), a combination which has not yet been described in familial cases of ALS-FTD.

MATERIALS AND METHODS

Mutation Analysis

Genomic DNA from cases V:2 and IV:6 was extracted from whole blood using standard protocols (PUREGENE DNA Purification Kit, Gentra Systems, Minneapolis, MN). Genetic testing for superoxide dismutase 1 (*SOD1*)-mediated

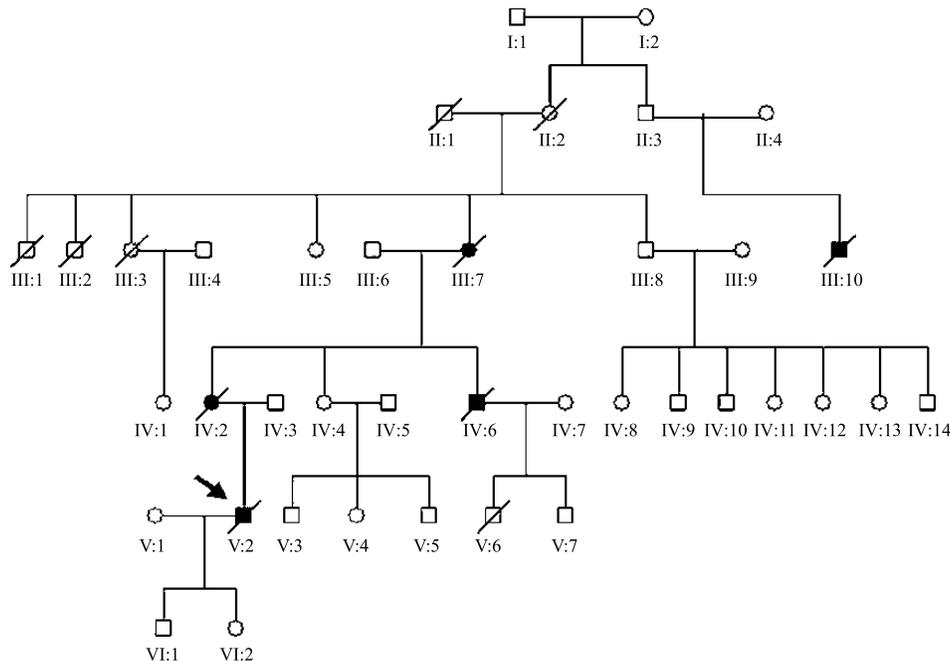


FIGURE 1. Pedigree of reported cases. Family pedigree showing the proband (V:2, arrow), his mother (IV:2) and uncle (IV:6). The proband’s grandparents were originally from the Azores Islands (Portugal). Squares denote males and circles females. Diagonal lines mark those who are deceased.

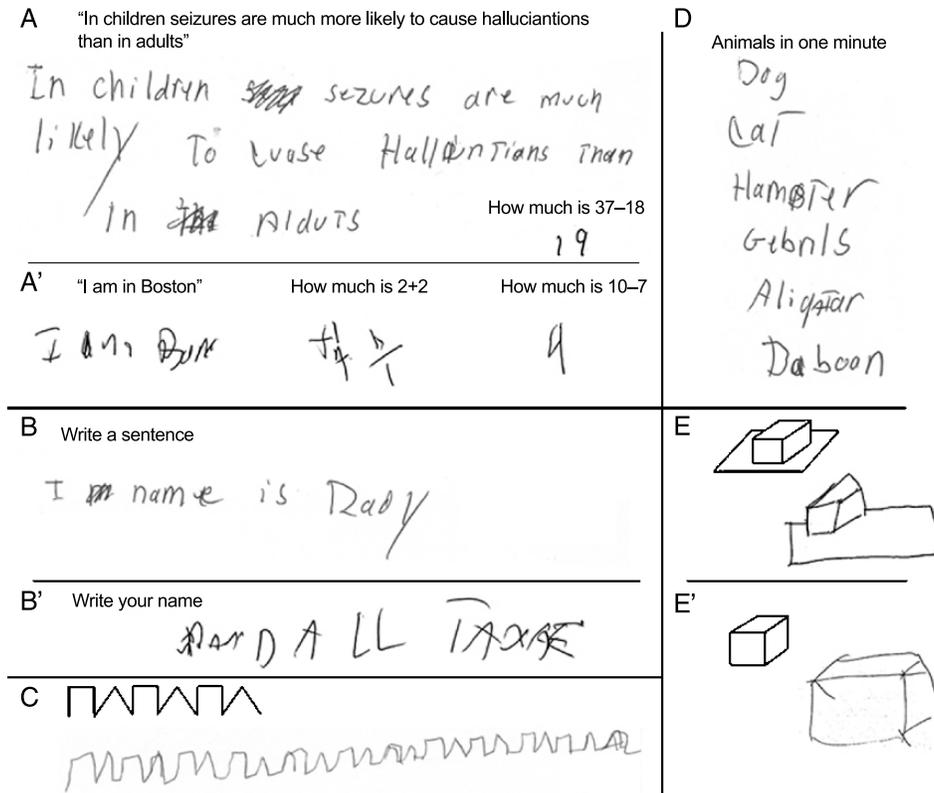


FIGURE 2. Language and cognitive deficits over time in the proband (V:2). **(A)** Dictation samples at the time of the proband's first visit to our office in February 2000 and again 9 months later in November 2000 **(A')**. **(B)** Sample written sentence in February 2000. When asked again to write a sentence 9 months later, he paused for a long time, but did attempt to write his name on command **(B')**. **(C)** Luria sequence in February 2000. **(D)** Written list of animals produced in the course of 1 minute in February 2000, when the proband was already mute. **(E)** Copy of 3-dimensional cubes in February 2000 and 6 months later **(E')**.

ALS, Huntington disease, and spinocerebellar ataxias SCA-1, 2, 3, 6, and 7 was performed by Athena Diagnostics (Worcester, MA). The microtubule-associated protein tau (*MAPT*) and chromatin modifying protein 2B (*CHMP2B*) genes were polymerase chain reaction (PCR)-amplified as previously described (8, 42), sequenced using a DTCS kit for dye terminator cycle sequencing (Beckman Coulter, Fullerton, CA), and analyzed using CEQ 8000 genetic analyzer (Beckman Coulter) following the manufacturer's protocol. The CAG trinucleotide repeat within the *DRPLA* gene was PCR amplified as described previously (43) with infrared dye-labeled primers (LI-COR Biosciences, Lincoln, NE), and the CAG allele size was determined using gel electrophoresis (LI-COR Biosciences) and Gene ImagIR software (Scanalytics, BD Biosciences, Rockville, MD).

Neurohistology

The following antibodies were used in the analysis of the neuropathologic material from the proband at the indicated dilutions: anti-tau (A0024 rabbit polyclonal, 1:8000; Dako, Glostrup, Denmark); anti- β -amyloid (M0872 mouse monoclonal clone 6F/3D, 1:150; Dako); anti- α -synuclein (ZS18-0215, mouse monoclonal 1:6000; Zymed, Invitrogen, Carlsbad, CA); and anti-ubiquitin (mouse monoclonal, 1:200; Novocastra, Vision BioSystems, Inc., Norwell, MA).

For ubiquitin immunostaining, antigen retrieval was performed in a pressure cooker using target unmasking fluid (Zymed). Other routine neuropathologic stains were performed according to standard protocols.

RESULTS

Clinical Description of Cases

The family pedigree is shown in Figure 1. The proband (V:2) was the most recently affected relative. Both of the proband's maternal grandparents were born in the Azores Islands. The other affected relatives were the proband's mother (IV:2) who died of ALS at age 34, his maternal uncle (IV:6) who died of ALS at age 37, and his maternal grandmother (III:7) who reportedly died of ALS at age 38. There was probably a fifth affected relative (III:10) because it is known that he had weakness with muscle wasting of the legs, diffuse fasciculations, and hyperreflexia.

Proband (V:2)

The patient was healthy until November 1998, when at the age of 31 he began stuttering and mispronouncing words, especially those that began with the letters "w" and "h." Within a few months his speech became hypophonic and

dysarthric, and he began confusing the words “yes” and “no” when answering questions. The speech problems progressed rapidly such that, by the fall of 1999, he could say a few isolated words but was unable to use full sentences. He communicated by writing in a pad, and his written language was initially intact. There were no obvious signs of dementia, but his wife had noted that when playing board games he began to make mistakes when counting. Neuropsychologic testing in December 1999 showed impaired information processing and abstract reasoning, consistent with frontal lobe dysfunction. His performance on Part B of the Trail-Making Test was in the severely impaired range, and he could not put the individual elements of a cartoon in the appropriate sequence.

When first evaluated by a neurologist in February 2000, he had almost complete aphonia. This was due predominantly to anarthria rather than to aphemias or aphasia, as his written language was relatively well preserved with normal naming and comprehension. He could only pronounce a few words such as “yes” and “no” or his name. He could not repeat even the simplest words or monosyllabic sounds and was unable to hum the tune to “Happy Birth-

day.” He had problems answering yes/no questions appropriately by nodding or shaking his head. He could write sentences but made occasional spelling errors (e.g. “remmeber” instead of “remember”; see also Fig. 2A, B). He showed motor impersistence with the written Luria sequence (Fig. 2C). There was no ideational or buccal-facial apraxia, and his tongue moved well from side-to-side. His memory for hidden objects was excellent, but verbal memory was poor. His drawing of a clock was perfect, but instead of drawing intercrossing pentagons he drew hexagons. He had difficulties with simple arithmetic. He also showed lack of insight into his disease and laughed excessively or inappropriately at times, suggesting a pseudo-bulbar affect, although he had no social disinhibition or inappropriate behavior. When he had difficulties performing a task, an initial smile would suddenly transfigure itself into a look that suggested psychic pain. The remainder of his neurologic examination was normal, with no evidence of upper or lower motor neuron disease and no features of parkinsonism.

In March 2000, he had extensive testing. Electromyography did not show signs of motor neuron disease. Brain

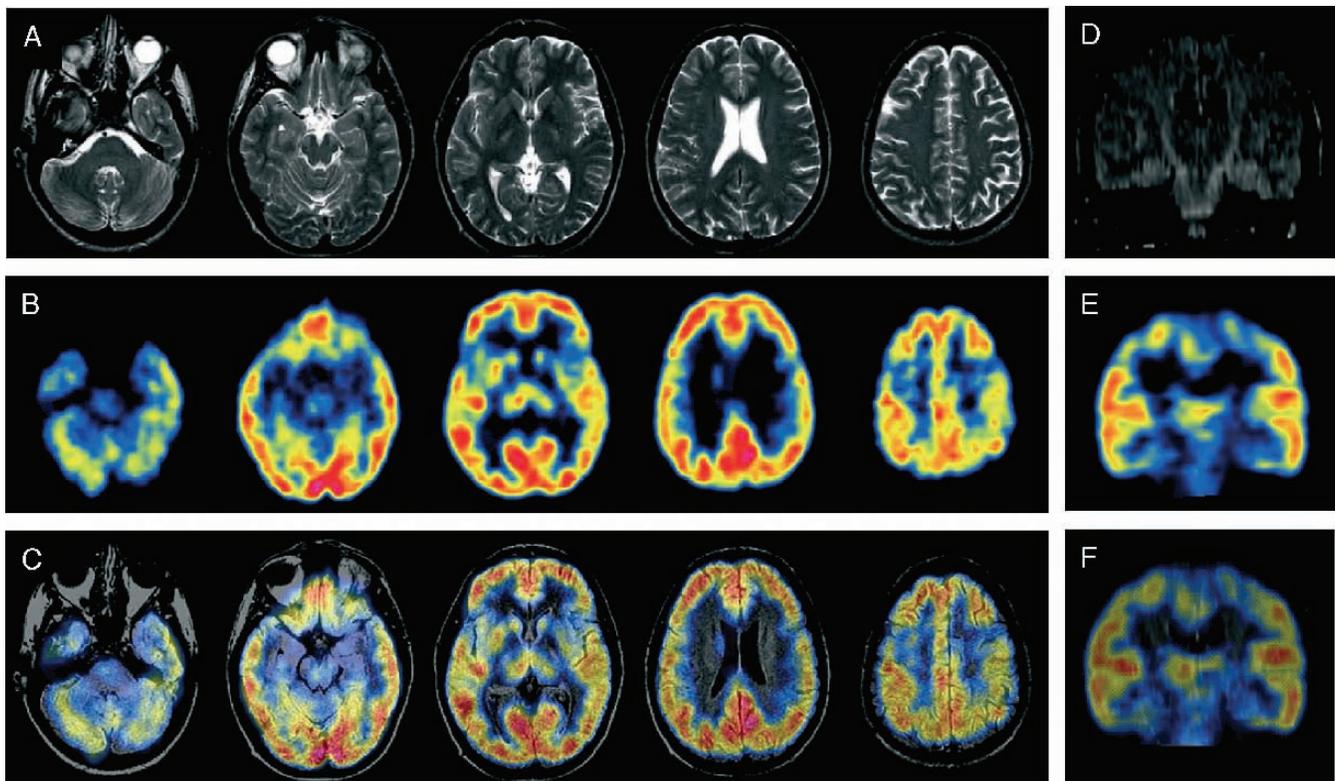


FIGURE 3. Structural and functional brain imaging in the proband (V:2). **(A)** T2-weighted brain magnetic resonance imaging (MRI) (axial images). **(B)** Fluorodeoxyglucose positron emission tomography (PET) scans of the brain (axial images). Note the asymmetric abnormal uptake (hypometabolism) in the frontal lobes, temporal lobes, and basal ganglia, with the left side being more affected. **(C)** Coregistration of fluid-attenuated inversion recovery (FLAIR) images from the brain MRI with the PET scan (axial images). **(D)** Coronal FLAIR image at the level of the internal capsule. Note the abnormal signal within the descending corticospinal tract bilaterally. **(E)** Coronal FDG-PET scan. Note the abnormal uptake within the temporal and parietal regions. **(F)** Coregistration of the coronal FLAIR image from the brain MRI with the corresponding FDG-PET image. For all panels, the left side of the image corresponds to the right hemisphere of the patient.

TABLE. Summary of Neuropathologic Findings in Pallidolysionigral Degeneration-Amyotrophic Lateral Sclerosis

Clinical Findings	Proband (V:2)	Maternal Uncle (IV:6)	Patient #1 (Ref. 37)	Patient #2 (Ref. 38)
Age at death, gender	34, male	40, male	35, female	34, female
Duration of illness	3 years	3 years	2 years	2 years
Cognitive impairment-dementia	Present	Absent	Absent	Absent
Parkinsonism-basal ganglia dysfunction	Present	Absent	Present	Present
Motor neuron disease	Present	Present	Present	Present
Neuropathologic findings	Neuronal loss/gliosis	Neuronal loss/gliosis	Neuronal loss/gliosis	Neuronal loss/gliosis
Upper motor neurons	+++/+	-/-*	+/-	-/-
Anterior horn cells of spinal cord†	++/+	+++/>+++	++/>++	+++/>+++‡
Clarke's column of spinal cord	NA	+++/>++	NA	NA
Intermediolateral cell column of spinal cord	NA	+++/>++	NA	NA
Brainstem motor nuclei	+++/>+++	+++/>+++	++/>++§	+/-§
Globus pallidus	+++/>+++	+++/>+++	+++/>+++	+++/>+++
Subthalamic nucleus	+++/>+++	+++/>+++	+++/>+++	++/>+++
Substantia nigra	++/>++	++/>++	+/>+	++/>++
Locus coeruleus	-/>-	-/>-	-/>-	-/>-
Caudate/putamen	+/>+++	-/>+	-/>-	-/>-
Thalamus	-/>-	-/>+++¶	-/>-	-/>-
Cerebral cortex and white matter	-/>-**	-/>-*	-/>-	-/>-
Cerebellar cortex, white matter, peduncles	-/>-	-/>-	-/>-	-/>-
Red nucleus	Mild neuronophagia	-/>-	NA	NA
Dentate nucleus	-/>-	-/>-	NA	NA
Inferior olivary nucleus	-/>-	-/>-	NA	NA
Colliculi	-/>-	-/>-	NA	NA
Periaqueductal gray	-/>-	-/>-	NA	NA
Basis pontis	-/>-	-/>-	NA	NA

Comparison between the neuropathologic findings in the proband (V:2), his maternal uncle (IV:6), and 2 previously reported sporadic cases with similar pathology (37, 38). Neuronal loss/gliosis: -, absent; +, mild; ++, moderate; +++, severe. NA, not applicable.

*, Neuronal loss in the cerebral cortex is not clearly evident with the exception of loss of Betz cells in the primary motor cortex.

†, Only the upper cervical cord was available from the proband.

‡, Greater loss in the cervical spinal cord than in the lumbar cord.

§, Only the hypoglossal nucleus was affected; other brainstem nuclei were normal.

||, Scattered extracellular neuromelanin pigment deposits were present.

¶, Gliosis in the centrum medianum of the thalamus.

**, Gliosis was mild in most of the cerebral cortex and moderate in the subcortical white matter. It was much more apparent on glial fibrillary acidic protein stains than by hematoxylin and eosin.

magnetic resonance imaging with magnetic resonance spectroscopy was normal except for fluid-attenuated inversion recovery images, which showed increased T2 signal within the corticospinal tract (Fig. 3). A fluorodeoxyglucose (FDG) positron emission tomography (PET) scan showed abnormal FDG uptake in portions of the temporal lobes, frontal lobes, and the basal ganglia bilaterally with a slight (left > right) asymmetry (Fig. 3). Cerebrospinal fluid was normal. Ceruloplasmin was normal. By May–June 2000 he was mute and had increasing difficulties communicating by writing. He made frequent spelling mistakes. His visual pursuits were abnormal, and he could not smile on command. He had developed an asymmetry in reflexes (being brisker on the right side). He had a right-sided pronator drift and slowness in finger tapping with the right hand. He also had new right-left confusion and prominent snout and palmomental reflexes.

By November 2000, 2 years after the initial symptoms, he had quit his job and was no longer driving a car. He had developed some dysphagia with liquids and required supervision and assistance with feeding. He was losing weight

rapidly, despite a voracious appetite. He had normal bladder and bowel control but had developed impotence. His written language had deteriorated further (Fig. 2A', B'). His visuospatial memory for hidden objects was still intact. Extraocular movements were full. His tongue protruded in the midline with normal strength, but it now had fasciculations. Jaw jerk was brisk, with clonus. He had decreased eye blinking, and the right-sided bradykinesia was still present. Walking, Romberg, and tandem gait were still normal, but he had difficulty maintaining his balance when turning, although he was not falling. By March 2001, he had become more withdrawn but still recognized his family. His emotional lability was triggered by the slightest stimulus, such as seeing a familiar face or listening to a particular song. His balance and gait had deteriorated significantly, and he was using a wheelchair outside his home to avoid falls. He was receiving both occupational and physical therapy.

By June 2001 he could no longer stand unsupported. He had marked hypomimia and generalized rigidity. His eye movements were no longer full. He now had urinary incontinence and constipation. A percutaneous endoscopic

gastrostomy tube was being considered because of constant coughing when being fed. In the last 5 months of his life his condition continued to deteriorate. He died at home in November 2001, 3 years after the onset of his symptoms.

Maternal Uncle (IV:6)

This man was in excellent health until May 1992 when he first noticed weakness of his left arm and occasional symptoms consistent with myotonia. When he was first examined 2 months later he had atrophy and weakness of his left supraspinatus, infraspinatus, triceps, and deltoid muscles, with prominent fasciculations in the same muscles, and hyperactive muscle stretch reflexes in the knees bilaterally. Electromyography showed fibrillation potentials in the left abductor digiti minimi (1+), first dorsal interosseous (1+), triceps (1+), biceps (2+), C5 and C6 paraspinal (2+), and deltoid (3+) muscles, but none in the legs. Laboratory testing was normal. By January 1993 he had developed severe weakness of the left upper extremity, and he was now experiencing weakness in the left leg. In July 1993, he had weakness in the proximal right arm and began using a cane because of frequent falls. He was beginning to experience dysphagia but had no speech difficulties. By September 1993 he had lost all use of his left arm and had significant swallowing problems. His neck was also weak, and he began to complain of orthopnea, requiring oxygen at night. By the end of November 1993 he required noninvasive means of ventilation. In February 1994 a percutaneous endoscopic gastrostomy tube was placed. Over the course of subsequent months he became wheelchair bound. At the time of his last neurology clinic visit, in June 1994, he had good use of his right arm and could still bear weight. His condition continued to deteriorate, and he died at age 40 of respiratory failure in May 1995, 3 years after the onset of his symptoms. He never manifested language deficits, cognitive difficulties, or parkinsonism.

Neuropathology

A summary of the neuropathologic findings is shown in the Table.

Proband (V:2)

The brain and the upper cervical spinal cord were available for examination. The brain, fixed in formalin, weighed 1,285 g. There was slight ventricular dilatation. In addition, there was slight discoloration and atrophy of the globus pallidus and subthalamic nuclei bilaterally. There was no evidence of atrophy of the cerebral cortex, and there was no grossly apparent thinning of the anterior spinal nerve roots.

At the microscopic level there were features of ALS, with both upper and lower motor neuron abnormalities. The density of Betz cells was decreased, and there was myelin loss involving the corticospinal tract at the mesencephalic basis pedunculi (Fig. 4A). There was moderate loss of anterior horn cells within the rostral cervical spinal cord (Fig. 4C) and a corresponding loss of axons within the anterior nerve roots. There was severe loss of neurons and associated gliosis within the hypoglossal nuclei (Fig. 4E, G) and abducens nuclei. In addition, there was mild gliosis and scattered neuronophagia

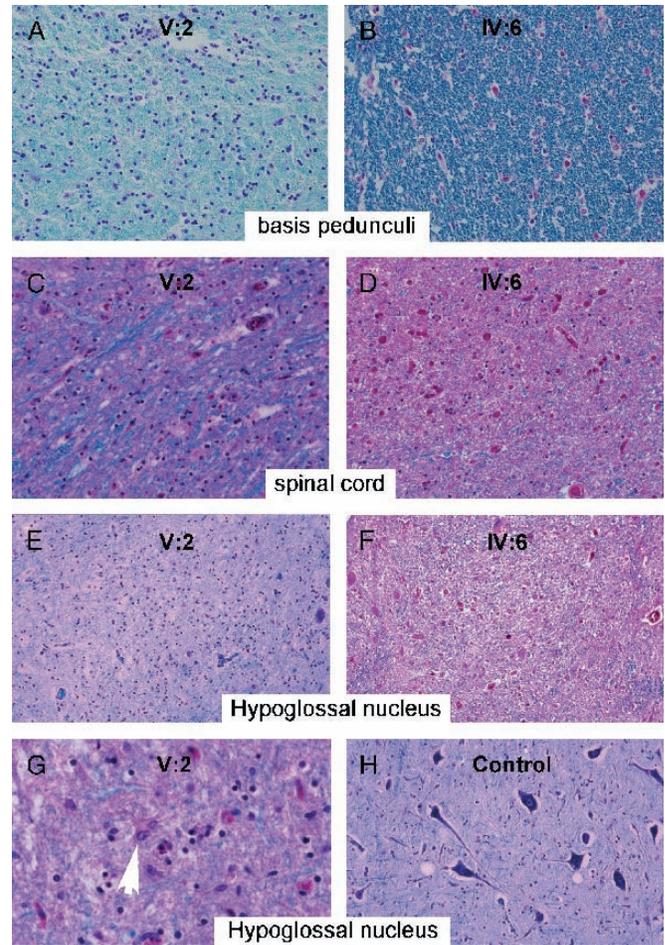


FIGURE 4. Comparison of neuropathology between the proband (V:2) and his uncle (IV:6). (A, B) Middle third of the mesencephalic basis pedunculi. Note the myelin pallor and marked gliosis in the proband (A) compared with the normal appearing tissue in the uncle (B). The lateral third of the basis pedunculi in the proband was less affected (not shown). These findings correlate with a loss of upper motor neurons in the proband but not in the uncle. (C, D) Anterior horn from the proband's cervical spinal cord (C) and anterior horn from the uncle's thoracic spinal cord (D). (E, F) Hypoglossal nucleus. Note the severe neuronal loss and gliosis in both the proband (E) and his uncle (F). (G) Higher magnification of the hypoglossal nucleus from the proband. Note the absence of large motor neurons and the reactive gliosis (microglia and astrocytes; arrowhead). (H) Hypoglossal nucleus from an age-matched control. V:2 indicates the proband, IV:6 indicates his maternal uncle, and Control indicates a normal individual, age-matched to the proband. A, B, E, and H and from sections stained with Luxol fast blue/Nissl (Klüver-Barrera). C, D, F, and G are from a section stained with Luxol fast blue/hematoxylin and eosin.

within the dorsal motor nuclei of the vagus nerve (not shown). The oculomotor nuclei were spared.

There was also evidence of PLND, with neuronal loss and gliosis within the globus pallidus (severe; Fig. 5A), subthalamic nucleus (severe; Fig. 5C, E) and the substantia nigra (moderate; Fig. 5G) with associated extracellular

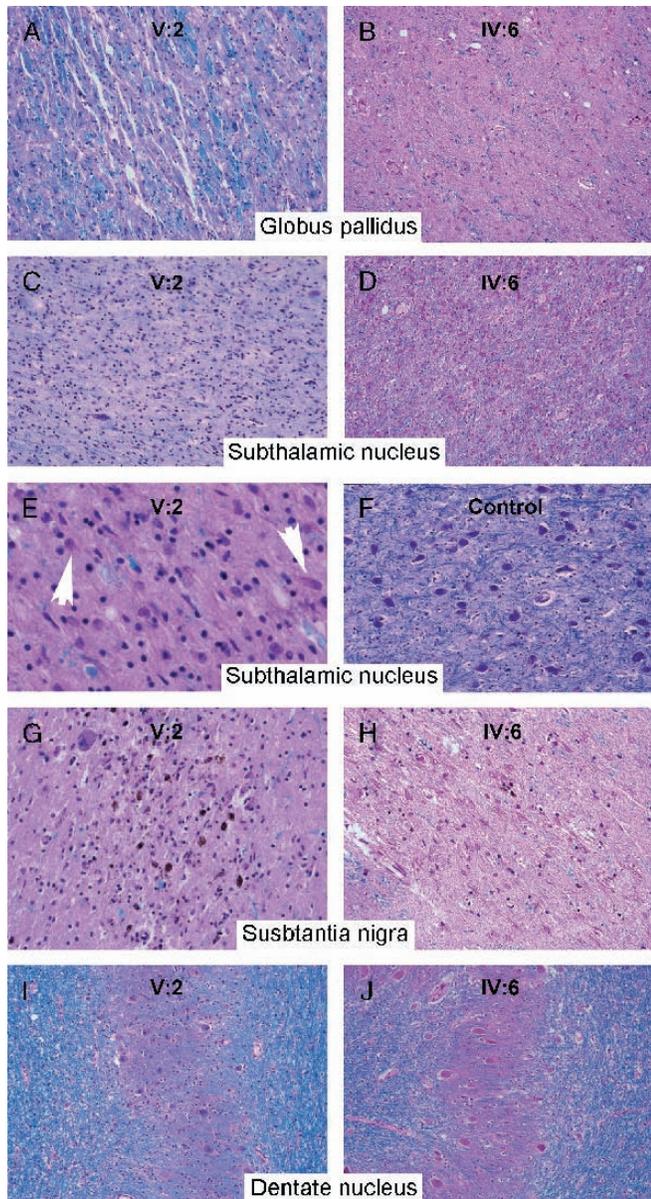


FIGURE 5. Additional neuropathology in the proband (V:2) and uncle (IV:6). **(A, B)** Globus pallidus, pars interna. There is near total neuron loss and marked gliosis in both the proband **(A)** and his uncle **(B)**. **(C, D)** Subthalamic nucleus. There is severe neuron loss and marked gliosis in both the proband **(C)** and his uncle **(D)**. **(E)** High-magnification view of the subthalamic nucleus in the proband. Note the severe neuronal loss and presence of reactive astrocytes (arrowheads). **(F)** Subthalamic nucleus from an age-matched control. **(G, H)** Substantia nigra. Note the similar degree (moderate-to-severe) of neuronal loss, deposition of extracellular neuromelanin, and gliosis in the proband **(G)** and his uncle **(H)**. **(I, J)** Dentate nucleus of the cerebellum. Tissue appears normal in both the proband and his uncle. V:2 indicates the proband, IV:6 indicates his maternal uncle, and Control indicates a normal individual, age-matched to the proband. All panels were from sections stained with Luxol fast blue/hematoxylin and eosin, except for **C** and **F**, which were from sections stained with Luxol fast blue/Nissl (Klüver-Barrera).

pigment deposition, but without Lewy bodies. The caudate nucleus and putamen showed severe gliosis and mild neuronal loss. Gliosis was also apparent in the claustrum (moderate) and the thalamus (mild). The red nucleus showed scattered neuronophagia. There was mild gliosis throughout the cerebral cortex and in the subcortical white matter. Pick bodies, neurofibrillary tangles, neuritic plaques, neuropil threads, or Lewy bodies were not found. Immunostains for tau and β -amyloid were negative in all portions of the nervous system examined. Immunostaining for ubiquitin showed high background but no consistent pattern of cytoplasmic staining in neurons. Immunostains for α -synuclein failed to reveal inclusions in neurons or glial cells in multiple blocks. There was no evidence of iron accumulation in any brain structures. The dentate nucleus of the cerebellum appeared normal (Fig. 5I). Other relevant negative findings are listed in the Table.

Maternal Uncle (IV:6)

The brain and spinal cord were available for examination. The brain, fixed in formalin, weighed 1,340 g. There was moderate atrophy and brown discoloration of the subthalamic nucleus and atrophy of the internal segment of the globus pallidus. There was mild pallor of the substantia nigra, but the locus coeruleus was normally pigmented. There was mild brown discoloration of the gray matter of the rostral cervical spinal cord and thinning of the anterior nerve roots at all levels. There was no evidence of atrophy of the cerebral cortex.

Histologically, there was no evidence of loss of upper motor neurons and no significant pallor of myelin stain in the cerebrospinal tracts in the brainstem (Fig. 4B). There was, however, evidence of severe neuronal loss and gliosis in the anterior horns of the spinal cord at all levels examined (Fig. 4D). No Bunina bodies could be identified in the remaining motor neurons. In addition, Clarke's columns and the intermediolateral cell columns were markedly degenerated. There was moderate neuronal loss and gliosis in the hypoglossal nuclei (Fig. 4F) and in the motor nuclei of the trigeminal nerve.

In addition to the motor neuron findings, there was neuronal loss and gliosis in the globus pallidus (moderate to severe; Fig. 5B), subthalamic nuclei (severe; Fig. 5D), and substantia nigra (moderate; Fig. 5H). There was associated loss of pigment in the substantia nigra but no evidence of Lewy bodies. The locus coeruleus was normal. There was gliosis in the nucleus centrum medianum of the thalamus (moderate to severe) and in the head of the caudate nucleus (mild) and to a lesser extent in the putamen. Importantly, there was no evidence of neurofibrillary tangles, neuritic plaques, or neuropil threads in any of the affected areas and no evidence of Pick bodies or ubiquitin-positive inclusions in the cerebral cortex or in the neurons of the stratum granulosum of the hippocampus. No argyrophilic, intracytoplasmic glial inclusions were identified in any area of the nervous system. There was no evidence of iron accumulation in any brain structures. The dentate nucleus of the cerebellum appeared normal (Fig. 5J). Other pertinent negative findings are listed in the Table.

Genetic Testing

Sequence analysis of the *SOD1* gene in cases IV:6 and V:2 failed to identify any novel or known mutations. Furthermore, sequence analysis of the *MAPT* and *CHMP2B* genes in case V:2 revealed no known or novel mutations. PCR analysis showed the length of CAG repeat alleles in case V:2 to be within a normal range in the following genes (allele sizes/number of repeats): *SCA1* (32, 36), *SCA2* (22, 23), *SCA3* (23, 27), *SCA6* (11, 15), *SCA7* (12, 16), *HD* (11, 17), and *DRPLA* (16, 16).

DISCUSSION

We have described a pedigree with a neurodegenerative disorder characterized by an unusual combination of clinical symptoms and neuropathologic features. The striking and unique characteristics of this pedigree include the combination of young age of onset and rapidly progressive course, together with variable initial clinical presentations (motor neuron disease vs primary progressive aphasia) but common neuropathologic abnormalities. The clinical features point to a diagnosis of ALS-FTD in the proband but the pathologic hallmarks of ALS-FTD were lacking. Instead, we found PLND and ALS, with complete sparing of deep cerebellar nuclei.

The combination of PLND and ALS is rare. In 1 autopsy series of 102 patients who had ALS clinically, 2 had associated PLND but without any clinical signs or symptoms attributable to this degeneration (34). If this series is taken to be representative, one might expect such an association in as many as 2% of all cases of ALS.

We are aware of a total of 9 reported cases of PLND and ALS with pathologic features similar to those seen in the present pedigree (34–41). Among those cases, there was wide variability in the duration of illness (range: 7–156 months) and age at the time of death (range: 34–67 years old). Interestingly, the 2 cases that are clinically and pathologically most similar to the ones we discuss here were those of 2 unrelated women who also died in their mid-30s (34 and 35 years of age, respectively), each after a brief 2-year illness (37, 38). Both of those patients also had a relative who developed a “parkinsonian” illness at a relatively young age (30 and 45 years old), suggesting that these cases may have derived from more extended pedigrees; but further details are not available. It is possible that the pedigree we have described and these 2 other potentially familial cases could share the same genetic defect. For comparison we have included details about the clinical history and neuropathologic findings in these 2 patients in the Table (please refer to Sudo et al [35] for a more extensive table comparing findings in 6 other sporadic cases of combined PLND and ALS).

In a review of PLND, Jellinger (44) postulated 4 nosologic categories: 1) pure pallidal atrophy; 2) pure pallidolusian atrophy; 3) extended forms of pallidal degeneration, including involvement of the striatum, substantia nigra, and/or subthalamic nucleus; and 4) variable combinations of categories 1 to 3, along with degeneration of other systems such as the motor system. The neuropathologic findings in

the present pedigree correspond to the fourth category of Jellinger.

Although most patients with PLND show signs and symptoms attributable to dysfunction of the basal ganglia, this is not always the case (34, 39). In the present pedigree, the proband developed rigidity, postural instability, hypomimia, and bradykinesia late in the disease. In contrast, the proband’s uncle was not reported to have such impairments. One possible explanation for the lack of signs or symptoms directly attributable to dysfunction of the basal ganglia in the uncle (as well as in other reported cases of combined PLND and ALS) might be a partial masking of these findings due to severe dysfunction of the motor system.

Despite their profoundly different clinical syndromes, our proband and his uncle had similar neuropathologic alterations, although with a few important differences (Table). One distinction was the preferential upper motor neuron involvement in the proband compared with his uncle, who showed primarily lower motor neuron disease. A second difference was the extent of cerebral cortical disease, with the proband showing gliosis throughout the cerebral cortex and subcortical white matter, whereas his uncle lacked significant pathologic changes in the cerebral cortex.

The multisystem degeneration in this family, when considered separately from the ALS-type histologic findings, raises the diagnostic possibility of dentatorubral-pallidolusian atrophy (DRPLA) (45–47). However, the classic degeneration of deep cerebellar nuclei in DRPLA was absent from the cases we presented. Our pedigree also lacked a history of epilepsy, choreoathetosis, or myoclonus that is typical of patients with DRPLA. Further, screening for the DRPLA CAG expansion in the proband was negative.

Some of the pathologic findings in the proband and his uncle also overlap with features of progressive supranuclear palsy (PSP), in particular the loss of neurons in the substantia nigra, globus pallidus, and subthalamic nucleus (48). However, there was a notable absence of changes in the periaqueductal gray matter and the dentate nucleus of the cerebellum. Moreover, neurofibrillary tangles are usually found in affected neurons in PSP, but they were absent in the 2 cases we present. In addition, the tau-positive glial inclusions characteristic of PSP were not identified in our cases. Lastly, neither the history nor the clinical examination supports a clinical diagnosis of PSP.

Although the pathology that we describe in the present cases resembles some aspects of the pathology of the ALS/parkinsonism-dementia complex of Guam, including neuronal loss in the anterior horns of the spinal cord, substantia nigra, and the basal ganglia (49, 50), that disorder is characterized by abundant neurofibrillary tangles, which were entirely absent from the brains of the patients discussed here.

The proband had motor neuron disease and dementia-like symptoms reminiscent of primary progressive aphasia. In addition, the FDG-PET revealed hypometabolism in the frontal and temporal lobes. The clinical presentation and the PET results are therefore suggestive of ALS-FTD. However, we feel that this diagnosis is unlikely in our cases for several reasons. First, the disease course in our cases was much too rapid, and there was no disinhibition. Importantly, the uncle

had no features of dementia at all. Second, PLND is not typically seen in patients with ALS-FTD. Even in a recently reported case of sporadic ALS-FTD with associated PLND (41), the patient was much older at the time of death (62 years) and had a longer clinical course (11 years). Third, the cerebral cortex is usually more severely affected in ALS-FTD than in our cases. Fourth, we did not identify ubiquitin-positive dystrophic neurites in the cerebral cortex or ubiquitin-positive cytoplasmic inclusions in the granule cells of the dentate gyrus, as is often found in ALS-FTD (32), even when PLND is present (41).

One of the interesting aspects of this pedigree is how the similarity of the pathologic findings between the proband and his uncle was in stark contrast to their different clinical phenotypes. Whereas the proband had deficits in language, cognitive, cerebellar, and basal ganglia systems, in addition to motor neuron disease at the end of his life, his uncle (and his mother) only had features of ALS. It is not uncommon for neurodegenerative disorders caused by a single gene defect to have a broad spectrum of clinical presentations. We screened for some of the known gene alterations associated with ALS, FTD, ALS-FTD, and common spinocerebellar ataxias (given the Azorean family origin) but found no abnormalities. We conclude that the autosomal dominant pattern of inheritance for the present pedigree is caused by a gene defect that remains to be defined. Further research with the aim of identifying additional similar cases will hopefully lead to the characterization of the genetic abnormality and ultimately to treatments or a cure for this devastating neurodegenerative disorder.

ACKNOWLEDGMENTS

We thank Drs. David N. Caplan and Yvette M. Bordelon for helpful discussions and/or comments on the manuscript. We also thank Dr. Matthew Frosch for his assistance in obtaining recuts on one of the cases and Dr. Keith Johnson for help with the PET-MRI coregistration.

REFERENCES

1. Finlayson MH, Martin JB. Cerebral lesions in familial amyotrophic lateral sclerosis and dementia. *Acta Neuropathol (Berl)* 1973;26:237-46
2. Hudson AJ. Amyotrophic lateral sclerosis and its association with dementia, parkinsonism and other neurological disorders: A review. *Brain* 1981;104:217-47
3. Neary D, Snowden JS, Mann DM, et al. Frontal lobe dementia and motor neuron disease. *J Neurol Neurosurg Psychiatry* 1990;53:23-32
4. Ringholz GM, Appel SH, Bradshaw M, et al. Prevalence and patterns of cognitive impairment in sporadic ALS. *Neurology* 2005;65:586-90
5. Lomen-Hoerth C, Murphy J, Langmore S, et al. Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology* 2003;60:1094-97
6. Lomen-Hoerth C, Anderson T, Miller B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology* 2002;59:1077-79
7. Talbot K, Ansorge O. Recent advances in the genetics of amyotrophic lateral sclerosis and frontotemporal dementia: Common pathways in neurodegenerative disease. *Hum Mol Genet* 2006;15(Suppl 2):R182-87
8. Skibinski G, Parkinson NJ, Brown JM, et al. Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. *Nat Genet* 2005;37:806-8
9. Munch C, Rosenbohm A, Sperfeld AD, et al. Heterozygous R1101K mutation of the DCTN1 gene in a family with ALS and FTD. *Ann Neurol* 2005;58:777-80
10. Mackenzie IR, Baker M, West G, et al. A family with tau-negative frontotemporal dementia and neuronal intranuclear inclusions linked to chromosome 17. *Brain* 2006;129:853-67
11. Ruddy DM, Parton MJ, Al-Chalabi A, et al. Two families with familial amyotrophic lateral sclerosis are linked to a novel locus on chromosome 16q. *Am J Hum Genet* 2003;73(2):390-96
12. Vance C, Al-Chalabi A, Ruddy D, et al. Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2-21.3. *Brain* 2006;129:868-76
13. Morita M, Al-Chalabi A, Andersen PM, et al. A locus on chromosome 9p confers susceptibility to ALS and frontotemporal dementia. *Neurology* 2006;66:839-44
14. Majoor-Krakauer D, Ottman R, Johnson WG, et al. Familial aggregation of amyotrophic lateral sclerosis, dementia, and Parkinson's disease: Evidence of shared genetic susceptibility. *Neurology* 1994;44:1872-77
15. Wilhelmsen KC, Lynch T, Pavlou E, et al. Localization of disinhibition-dementia-parkinsonism-amyotrophy complex to 17q21-22. *Am J Hum Genet* 1994;55:1159-65
16. Hosler BA, Siddique T, Sapp PC, et al. Linkage of familial amyotrophic lateral sclerosis with frontotemporal dementia to chromosome 9q21-q22. *JAMA* 2000;284:1664-69
17. Ostojic J, Axelman K, Lannfelt L, et al. No evidence of linkage to chromosome 9q21-22 in a Swedish family with frontotemporal dementia and amyotrophic lateral sclerosis. *Neurosci Lett* 2003;340:245-47
18. Staal A, Went LN. Juvenile amyotrophic lateral sclerosis-dementia complex in a Dutch family. *Neurology* 1968;18:800-6
19. Lomen-Hoerth C. Characterization of amyotrophic lateral sclerosis and frontotemporal dementia. *Dement Geriatr Cogn Disord* 2004;17:337-41
20. Robles A, Vilarino I, Sesar A, et al. Progressive degenerative aphasia: Clinical and neuroradiological observations in 18 cases. *Rev Neurol* 1997;25:505-12
21. Lynch T, Sano M, Marder KS, et al. Clinical characteristics of a family with chromosome 17-linked disinhibition-dementia-parkinsonism-amyotrophy complex. *Neurology* 1994;44:1878-84
22. Roberson ED, Hesse JH, Rose KD, et al. Frontotemporal dementia progresses to death faster than Alzheimer disease. *Neurology* 2005;65:719-25
23. Vercelletto M, Ronin M, Huvet M, et al. Frontal type dementia preceding amyotrophic lateral sclerosis: A neuropsychological and SPECT study of five clinical cases. *Eur J Neurol* 1999;6:295-99
24. Tsuchiya K, Ozawa E, Fukushima J, et al. Rapidly progressive aphasia and motor neuron disease: A clinical, radiological, and pathological study of an autopsy case with circumscribed lobar atrophy. *Acta Neuropathol (Berl)* 2000;99:81-7
25. Catani M, Piccirilli M, Geloso MC, et al. Rapidly progressive aphasic dementia with motor neuron disease: A distinctive clinical entity. *Dement Geriatr Cogn Disord* 2004;17:21-28
26. Janssen JC, Warrington EK, Morris HR, et al. Clinical features of frontotemporal dementia due to the intronic tau 10(+16) mutation. *Neurology* 2002;58:1161-68
27. Kertesz A, Hudson L, Mackenzie IR, et al. The pathology and nosology of primary progressive aphasia. *Neurology* 1994;44:2065-72
28. Nakano I. Frontotemporal dementia with motor neuron disease (amyotrophic lateral sclerosis with dementia). *Neuropathology* 2000;20:68-75
29. Mann DM, South PW. The topographic distribution of brain atrophy in frontal lobe dementia. *Acta Neuropathol (Berl)* 1993;85:334-40
30. Mann DM, South PW, Snowden JS, et al. Dementia of frontal lobe type: Neuropathology and immunohistochemistry. *J Neurol Neurosurg Psychiatry* 1993;56:605-14
31. Morris J. Frontotemporal dementias. In: Clark CM, Trojanowski JQ, eds. *Neurodegenerative Dementias: Clinical Features and Pathological Mechanisms*. New York: McGraw-Hill, 2000:278-90
32. Forman MS, Farmer J, Johnson JK, et al. Frontotemporal dementia: Clinicopathological correlations. *Ann Neurol* 2006;59:952-62
33. Brown R. Amyotrophic lateral sclerosis with dementia: A review. In: Clark CM, Trojanowski JQ, eds. *Neurodegenerative Dementias: Clinical Features and Pathological Mechanisms*. New York: Mc Graw-Hill, 2000:367-72
34. Piao YS, Wakabayashi K, Kakita A, et al. Neuropathology with clinical correlations of sporadic amyotrophic lateral sclerosis: 102 autopsy cases examined between 1962 and 2000. *Brain Pathol* 2003;13:10-22

35. Sudo S, Fukutani Y, Matsubara R, et al. Motor neuron disease with dementia combined with degeneration of striatonigral and pallidolusian systems. *Acta Neuropathol (Berl)* 2002;103:521–25
36. Bergmann M, Kuchelmeister K, Migheli A, et al. Motor neuron disease with pallido-lusio-nigral atrophy. *Acta Neuropathol (Berl)* 1993;86:105–8
37. Gray F, De Baecque C, Serdaru M, et al. Pallido-lusio-nigral atrophy and amyotrophic lateral sclerosis. *Acta Neuropathol Suppl (Berl)* 1981;7:348–51
38. Gray F, Eizenbaum JF, Gherardi R, et al. Luyso-pallido-nigral atrophy and amyotrophic lateral sclerosis. *Acta Neuropathol (Berl)* 1985;66:78–82
39. Hasegawa K, Kowa H, Yagishita S. Extrapyramidal system involvement in motor neuron disease. *J Neurol Sci* 1992;108:137–48
40. Kato S, Oda M, Murahashi M, et al. Motor neuron disease with involvement of the pallido-lusio-nigral system and mesencephalic tegmentum. *Clin Neuropathol* 1995;14:241–44
41. Toyoshima Y, Tan CF, Kozakai T, et al. Is motor neuron disease-inclusion dementia a forme fruste of amyotrophic lateral sclerosis with dementia? An autopsy case further supporting the disease concept. *Neuropathology* 2005;25:214–19
42. Poorkaj P, Bird TD, Wijsman E, et al. Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Ann Neurol* 1998;43:815–25
43. Komure O, Sano A, Nishino N, et al. DNA analysis in hereditary dentatorubral-pallidolusian atrophy: Correlation between CAG repeat length and phenotypic variation and the molecular basis of anticipation. *Neurology* 1995;45:143–49
44. Jellinger K. Extrapyramidal disorders. In: *Handbook of Clinical Neurology*. New York: Elsevier, 1986:445–63
45. Naito H, Tanaka M, Hirose Y, et al. Study on two autopsied cases of degenerative type of myoclonus epilepsy with choreo-athetoid movement: Proposal of hereditary dentate and pallidal system atrophy (Author's translation). *Seishin Shinkeigaku Zasshi* 1977;79:193–204
46. Naito H, Oyanagi S. Familial myoclonus epilepsy and choreoathetosis: Hereditary dentatorubral-pallidolusian atrophy. *Neurology* 1982;32:798–807
47. Kanazawa I. Dentatorubral-pallidolusian atrophy or Naito-Oyanagi disease. *Neurogenetics* 1998;2:1–17
48. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy: A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy: Nuchal dystonia and dementia. *Arch Neurol* 1964;10:333–59
49. Hirano A, Malamud N, Elizan TS, et al. Amyotrophic lateral sclerosis and Parkinsonism-dementia complex on Guam: Further pathologic studies. *Arch Neurol* 1966;15:35–51
50. Kurland LT, Hirano A, Malamud N, et al. Parkinsonism-dementia complex, an endemic disease on the island of Guam: Clinical, pathological, genetic and epidemiological features. *Trans Am Neurol Assoc* 1961;86:115–20