ABSTRACT: A 56-year-old man presented with gait disturbance, personality change, and behavioral disturbances. He subsequently developed falls, postural instability, and axial rigidity. The cognitive problems progressed and he developed aphasia and later eye movement abnormalities. He died after 9 years of disease. Experts discuss the syndromal diagnosis and predict the underlying pathology. The pathological diagnosis is given and clinical learning points are considered. © 2011 Movement Disorder Society

Key Words: frontotemporal dementia; corticobasal degeneration; progressive supranuclear palsy; clinicopathological case

Clinical History (Andrew Evans and David Williams)

This 56-year-old man initially presented to his local doctor with gait disturbance and a tendency to stoop forward. He had no significant past medical history. His father died with cancer at 63 years of age and his 84-year-old mother and sister were well. He had an aunt who developed Alzheimer’s disease in her late 70s and died in her early 80s.

No diagnosis was made and no treatment was initiated after the first visit. His family encouraged him to return to the local doctor around 8 months later because of slight deterioration in his walking and a change in his personality. He had become more aggressive and was prone to impulsive shopping and alcohol binges. He had previously not regularly consumed alcohol and was a conservative but social member of his local community. Over the next few months, the personality changes progressed, and he started to gain weight from over eating, with a particular predilection for sweet foods. He also had some word finding difficulties and was referred to a psychiatrist. The psychiatrist noted some dysphasia and no affective disorder. He had mild symmetrical bradykinesia in the limbs but no rigidity or tremor. Although he reported balance disturbance, he did not have postural instability on pull testing and had not fallen.

No treatment was started and over the next 3 years, his balance worsened and although his symptoms remained slowly progressive, he continued working. He eventually stopped working as a clerk because of reduced mobility and work performance because of cognitive decline. By the age of 61, 5 years after disease onset, he started falling. At that stage, he had axial rigidity, but no limb rigidity, no tremor, and still only mild bradykinesia. His postural reflexes were impaired and he walked with a flexed posture. He had
some urinary frequency but no other symptoms of autonomic dysfunction. By 62 years of age he was falling backward, at least weekly. He developed some nocturnal urinary incontinence. There was no measurable response to test doses of levodopa (L-dopa) and apomorphine.

He was eventually referred to a neurological specialty center and assessed. At that stage, 7 years after disease onset, he had global cognitive decline, with a verbal IQ of 83 and performance IQ of 85. The mini mental state examination score was 18/30. There was marked palilalia and perseveration. He demonstrated utilization behavior and magnetism. He did not report visual hallucinations. There were severe bradyphrenia and primitive reflexes were present. His hand writing was small. There was hypomimia, frontalis overactivity, and blepharospasm. Muscle tone was increased more in the midline more than in the limbs, and he had a moderately severe retrocollis. The family reported episodes analogous to oculogyric crises, lasting for up to 2 minutes, where his eyes would involuntarily look upward, and while extending his neck. Intercritically he had supranuclear palsy, with absent voluntary downgaze and reduced movement to the left and up. These restrictions were completely overcome with by the doll’s head maneuver. There was a long latency between command and generation of saccades in all directions.

He became severely bradyphrenic and virtually anarthric. He died at 65 years of age, after being fully dependent on others for care in the final 2 years.

Routine blood tests including thyroid function tests and thyroid antibody screen were normal. Cerebrospinal fluid examination was within normal limits. Nerve conduction studies and needle electromyography were normal. Electroencephalography showed dominant rhythm with intermittent frontotemporal abnormalities. A CT brain scan showed cerebral atrophy most conspicuous in the temporal lobes, without prominent deep white matter changes.

### Discussant 1 (Francisco Cardoso)

This man has developed a relentlessly progressive illness characterized by a combination of motor, behavioral, and cognitive abnormalities with a presenile onset, lasting 9 years until death. A parkinsonian syndrome was present since the onset, characterized by stooped posture and gait abnormality. With progression of the ailment, other features became noticeable including axial rigidity, bradykinesia, micrographia, postural instability, and severe dysarthria. Only later in the course of the illness was a mild rest tremor noticed. Dopaminergic treatment with L-dopa and apomorphine failed to improve the parkinsonism. The patient also had supranuclear ophthalmoparesis, more prominent on downgaze and recorded 7 years after the onset of the illness. The patient possibly had oculogyric crises, although this neuro-ophthalmologic finding was not observed by the patient’s physicians. Dystonia, characterized by retrocollis, and blepharospasm was also another movement disorder developed by the patient. In contrast and of note, the patient had no evidence of meaningful dysautonomia or cerebellar abnormality.

The patient also displayed severe behavioral and cognitive changes related to frontal lobe dysfunction. There was the development of impulse control disorder with overeating, shopping binges, and alcohol abuse. The patient also became demented with features suggestive of cortical dysfunction, such as word finding abnormality, and others compatible with subcortical lesion (bradyphrenia). In any case, both findings can be related to frontal lobe dysfunction. The latter hypothesis is further supported by existence of primitive reflexes, magnetism, utilization behavior, and perseveration. In the context of neuropsychiatric abnormalities, it is important to emphasize that he never had hallucinations.

Several diseases can lead to the combination of findings developed by this patient. The first that I shall consider is postencephalitic parkinsonism. Classically described as a complication of Von Economo’sencephalitis lethargica, which plagued Europe in the early years of the 20th century, it has also been related to other encephalitides. Typically, after the acute illness, there is an asymptomatic period followed by the development of a progressive disorder characterized by parkinsonian syndrome exquisitely sensitive to L-dopa associated with other features such as oculogyric crisis, supranuclear ophthalmoparesis, eyelid dystonia, tics, and behavioral abnormalities, although dementia is a rare feature. Interestingly, despite being secondary to external agent, this condition is known to be a tauopathy. Obviously, the clinical picture of this patient with lack of history of previous encephalitis, prominent dementia, and no response to L-dopa does not correspond to postencephalitic parkinsonism.

Two other tauopathies, however, can account for most, if not all, clinical features displayed by this patient. In a series of 245 patients with frontotemporal dementia (FTD), the median age at onset was 58 years, family history of a dementing illness was reported by 43% of patients, most patients developed a rigid-akinetic form of parkinsonism, prominent temporal atrophy was recorded in 40% of patients, and death occurred after a median duration of symptoms of 6.9 years. Classical features of this condition include marked disinhibition, dysexecutive dysfunction, and other signs of frontal lobe dysfunction. Another study has shown that patients with FTD display saccade impairments similar to those found in subjects with progressive supranuclear palsy (PSP). On
the other hand, rigid-akinetic syndrome with early postural instability and nonresponsive to l-dopa, associated with vertical supranuclear ophthalmoparesis, eyelid dystonia and subcortical dementia with marked frontal dysfunction is consistent with the Richardson variant of PSP. Nevertheless, the severe behavioral abnormalities and frontal lobe atrophy are more often found in FTD. When seen as a contender, as significant cognitive dysfunction is not a primary feature of multiple system atrophy. However, a pre-empted course prominent supranuclear gaze palsy and cognitive dysfunction is a contender. Nevertheless, it is expected that the autopsy showed findings of FTD, i.e., neuronal loss particularly marked in the frontal and temporal lobes, basal ganglia, and upper brainstem, with the presence of three repeat tau accumulations in neurons and to a lesser degree in astrocytes.

Syndromal diagnosis: FTD.
Pathological prediction: Three repeat tauopathy (Pick’s disease).

Discussant 2 (John Hodges)

The presentation of this 56-year-old man with gait disturbance and the subsequent development of a supranuclear gaze palsy immediately raises the possibility of PSP yet personality change was also prominent from an early stage, and there are a number of other features unusual for PSP. The impulsive behavior with aggression, binge eating, weight gain, and a predilection for sweet food are all highly characteristic of orbitofrontal dysfunction, most commonly seen in the context of behavioral variant FTD. To support this early syndromic diagnosis, a psychiatrist noted dysphasia. It would have been very useful to know more about the nature of the language disorder. Was this, for instance, the motor speech output disorder characteristic of progressive nonfluent aphasia, or the empty anomic aphasia without phonological or syntactic an error which typifies semantic dementia? Adynamism of speech with impoverished language output, but without language errors, is typical of PSP yet true aphasia against the diagnosis. After the initial cognitive presentation, motor features developed in earnest with falling, axial rigidity, and impaired postural reflexes. The lack of response to l-dopa and apomorphine is not particularly helpful in this context as this would be the characteristic of patients with FTD and parkinsonism, as well as most patients with PSP. Although a relatively good response to dopamine therapies has been found in the subgroup of PSP patients presenting with asymmetric onset and tremor typically who do not have cognitive problems. The absence of autonomic features rules out multiple system atrophy but this was never a serious diagnostic contender as significant cognitive dysfunction is not characteristic of multiple system atrophy. When seen in the specialist clinic, he had clear-cut dementia with a mini-mental state examination of 18/30 putting him in the moderately severe category. I would like to know more about the cognitive profile. PSP is associated with frontal executive deficits and memory retrieval problems but not aphasia. Although a subcortical dementia syndrome is extremely common in PSP, if not ubiquitous, it is very unusual for PSP patients to be so overtly demented. The examination findings at this stage were typical of PSP with severe axial rigidity, retrocollis, episodes of oculogyric crises, and a supranuclear gaze palsy involving predominately vertical eye movements. The investigations were rather noncontributory. The key investigation would have been an MRI with coronal images, which in FTD invariably reveals atrophy of the orbitofrontal cortex, medial paracingulate region, or anterior temporal lobes. We are informed that the CT scan showed temporal lobe atrophy which I am assuming implies cortical rather than hippocampal involvement but either would be very unusual for PSP.

In summary, the main differential remains PSP with unusually severe cognitive impairment versus a FTD with a typically pronounced motor features. Of the subtypes of PSP, the clinically phenotype recently named Richardson’s syndrome with a more aggressive course prominent supranuclear gaze palsy and cognitive dysfunction is a contender. However, a presentation with positive behavioral disturbances (disinhibition, impulsivity, and overeating) rather than apathy veers me toward a diagnosis of FTD. Disinhibition can occur in PSP but apathy is far more common. The early dysphasia, the severity of the dementia, and the temporal lobe atrophy is, I feel, more in keeping with FTD.

Within the spectrum of FTDs, a broad distinction can be made between those with underlying tau pathology versus those with the newly discovered TDP-43 protein abnormalities, labeled previously with ubiquitin and termed FTD-U. The combination in this case of severe cortical pathology with features of PSP is much more in keeping with an underlying tauopathy. Patients with overlapping features of PSP and FTD have been reported in the context of familial FTD and parkinsonism linked to chromosome 17 associated with mutations of the microtubule-associated protein tau (MAPT) gene, although there are also occasional reports of this combination with FTD-U. There was no clear family history in the case although his father died at 63 with cancer, which could have masked the onset of dementia.

In conclusion, I believe this to be the form of FTD associated with an underlying tau pathology and possibly a MAPT gene mutation.

Syndromal diagnosis: FTD.
Pathological prediction: Tauopathy, MAPT gene mutation.
Pathological Findings
(Tamas Revesz)

The brain showed atrophy that was most severe in the superior and lateral aspects of the frontal and temporal lobes and also the anterior parietal lobe. Coronal brain slices demonstrated marked dilatation of the entire lateral ventricle. The frontal cortical ribbon was thin, but the underlying white matter was only slightly reduced in bulk. The caudate and putamen were slightly atrophic and the globus pallidus was shrunken with orange/brown discoloration particularly involving the internal segment. In the midbrain, there was very little pigment remained in the substantia nigra and locus coeruleus was also palely pigmented. No other macroscopic abnormalities were noted in the pons, medulla, and cerebellum.

At microscopic examination, routine stains showed superficial spongiosis in the frontal cortex. Tau immunohistochemistry demonstrated neurofibrillary tangles, pretangles, numerous relatively short and broad threads, scattered structures composed of annular arrays of tau-positive short, stubby processes corresponding to astrocytic plaques, and numerous coiled bodies in oligodendroglial cells in all neocortical areas (Fig. 1A, 1B). The cortical tau pathology was most severe in the anterior frontal region. The subcortical white matter also contained numerous threads and coiled bodies. There were neurofibrillary tangles in all hippocampal subregions and the granule cells of the dentate fascia, subiculum, and parahippocampal cortex. There was no Aβ deposition, cortical Lewy bodies, or inclusions associated with frontotemporal lobar degeneration (FTLD) with ubiquitin-positive (tau negative) inclusions.

The striatum was affected by numerous threads, neurofibrillary tangles, mostly pretangles and occasional astrocytic plaques, but not by tufted astrocytes. The globus pallidus showed neurofibrillary tangles and pretangles and coiled bodies. There were threads and coiled bodies in the internal capsule. The subthalamic nucleus was preserved in bulk, but its neurons frequently contained neurofibrillary tangles and threads. There were neurofibrillary tangles in the thalamus.

There was significant loss of neurons in the substantia nigra with pigment incontinence and astrogliosis (Fig. 1C). Several of remaining nigra neurons contained neurofibrillary tangles and threads were also frequent (Fig. 1D). The neuron population of the locus coeruleus was relatively well preserved but it contained neurofibrillary tangles. The cerebellar cortex showed mild loss of Purkinje cells, but the dentate nucleus had a well-preserved neuronal population. There were numerous threads and pretangles in the cerebellar dentate.

Pathological Summary: This is a tauopathy with neurofibrillary tangles, pretangles and numerous threads in cortical, basal ganglia and brainstem, and cerebellar nuclei together with filamentous tau inclusions in glial cells. Both neuronal and glial tau pathology are seen in four-repeat tauopathies, which include PSP, corticobasal degeneration, variants of FTD with parkinsonism linked to chromosome 17 (FTDP-17T), and argyrophilic grain disease. The absence of a family history makes FTDP-17T unlikely and the lack of gran pathology excludes argyrophilic grains disease. Cortical involvement by tau pathology was a prominent feature of this case. The significance of this is that cortical pathology is, in general, considerably severe in corticobasal degeneration, while the deep gray matter and brain stem are the predominantly affected regions in PSP. It is of note, however, that PSP pathology is known to occasionally present with a corticobasal syndrome associated with severe cortical tau pathology are well documented. In progressive supranuclear cases, however, the characteristic astrocytic glial pathology is the tufted astrocyte, which was absent in this case. Therefore, the severe cortical tau pathology with numerous neurofibrillary tangles and pretangles, astrocytic plaques, and severe thread pathology are in favor of the diagnosis of corticobasal degeneration.

Pathological diagnosis: Corticobasal degeneration.

Learning Points (David Williams)

- Patients who develop FTD associated with parkinsonism, limb apraxia, or gait disturbance, the most likely underlying pathology is corticobasal degeneration.

All FTDs are characterized by changes in personal and social conduct, disinhibition, and disorders of language of varying degrees and are caused by FTLD. This group of pathologically defined diseases can be divided into tauopathies (corticobasal degeneration, PSP, Pick’s disease, argyrophilic grain disease, and FTD with associated parkinsonism linked to chromosome 17) or TDP-43 proteinopathies (previously classified as FTLD-U and including motor neuron disease, progranulin gene mutations, and other rare familial causes). A system of classifying FTD patients according to the dominant clinical feature at the time of presentation has emerged and includes the subgroups: behavioral variant FTD, progressive nonfluent aphasia, semantic dementia, FTD motor neurone disease, and corticobasal syndrome/parkinsonism. This system and its pathological correlates were tested in a large autopsy series with retrospective clinical assessment.
The group of “corticobasal syndrome” included patients with prominent limb apraxia, gait disturbance, or parkinsonism but was not limited to patients fulfilling proposed diagnostic criteria for corticobasal degeneration. In this study, patients with FTD who had coexistent prominent limb apraxia, gait disturbance, or parkinsonism were much more likely to have tau-positive pathology than TDP-43 positivity. Corticobasal degeneration (CBD) pathology was the most common pathology in this group, rather than Pick’s disease or argyrophilic grain disease. Language problems are common in these patients, and many with CBD develop progressive language output disorder or progressive nonfluent aphasia.

- Corticobasal syndrome is characterized by prolonged latencies to initiation of horizontal saccades.

Disorders of ocular motility have been documented in patients with corticobasal syndrome, and in the clinic, they can often be misinterpreted as signs typical of PSP. Several studies using electro-oculography have demonstrated abnormally increased latency to onset of saccadic eye movements in patients with corticobasal syndrome. Typically, the eye movement abnormalities are more severe on looking to the side where the apraxia predominates. Importantly, the saccadic velocity is usually normal in these patients and this important observation differentiates corticobasal syndrome from classic PSP. Unlike PSP and multiple system atrophy, square wave jerks are not seen. In corticobasal syndrome, there is an increased percentage of errors in the antisaccade task, probably as a result of frontal lobe pathology. In advancing disease patients with corticobasal syndrome can develop some mild slowing of saccadic velocity, although not as severe in advanced PSP. In the present patient, the saccadic latencies were severely delayed (Supporting Information Video) and when saccades were generated, they were moderately slowed. Saccadic latencies are said to remain normal in PSP, until complete ophthalmoplegia develops.

**Legends to the Video**

The patient is shown near the end of the disease with severe extrapyramidal tone. Grasp reflexes,
magnetism, utilization behaviors, and perseveration were demonstrated. The patient had reduced blink rate and hypomimia. Time to initiation of voluntary saccades was severely prolonged, and saccades were slow and reduced in amplitude. Smooth pursuit eye movements were restricted in the vertical plane but corrected with the doll’s eye maneuver. The patient walked with a stiff, narrow-based unsteady gait with shortened stride length and was prone to spontaneous falls.

References