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# Non-Fluent Progressive Aphasia, Depression, and OCD in a Woman With Progressive Supranuclear Palsy: Neuroanatomical and Neuropathological Correlations

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This paper details the case of a 64-year-old woman who presented to the psychiatry service with worsening mood in the context of a diagnosis of obsessive-compulsive disorder (OCD). On further examination she was found to have clinical findings consistent with frontotemporal lobar degeneration of the non-fluent progressive aphasia subtype. At post-mortem she was found to have progressive supranuclear palsy. We argue, in retrospect, that her OCD was likely prodromal to the development of her dementia. This case highlights the fact that frontotemporal lobar degeneration/progressive supranuclear palsy (FTLD/PSP) and other "tauopathies" represent a complex group of neurodegenerative disorders that may masquerade for many years as refractory psychiatric disorders.

## Case history

Mrs. A is a 64-year-old right-handed woman who had a long history of obsessive-compulsive disorder (OCD) which began in her mid 40s. Her primary symptoms of OCD were hand washing, showering, cleaning, and symmetry. Her OCD symptoms were so severe that they caused the dissolution of her marriage in the 1990s, and she subsequently lived alone in her own home. Over the year prior to her December 2003 admission she developed symptoms of depression, and her outpatient psychiatrists tried multiple high dose selective serotonin reuptake inhibitors (SSRIs) that helped her OCD symptoms to a significant extent but failed to adequately treat her depression. She was fully independent in her activities of daily living until six months prior to admission.

Her son, who saw his mother regularly, noted that over the six-month period prior to admission she had begun to exhibit increasing signs of inability to care for herself. He noted that she had begun to neglect some activities of daily living (ADLs) and he often found her sitting at home unable to motivate herself to do things. He cited as a further example that she used to take great pleasure in playing with her grandchildren and spending time with them, but of late she had begun to avoid such contacts and preferred to remain alone at home. He noted that over the two months prior to admission, she had worsening mood, decreased energy, decreased interest, anhedonia, and further declining ability to perform her ADLs.

She was referred by her outpatient psychiatrist for inpatient treatment of worsening depression and possible consideration for electroconvulsive therapy (ECT). On presentation to the hospital, she endorsed a worsening sense of depression accompanied by loss of interest in her life but without suicidal ideation. At the time of admission she was noted to be blunted in affect with profound psychomotor retardation. Her Folstein Mini-Mental State Exam (Folstein, Robins, & Helzer, 1983) score was 23 out of 30. On her neurological exam, cranial nerves II-XII were intact, and she had normal tone 5/5 strength in all her extremities except for weakness in left ankle dorsiflexion, which was longstanding and secondary to an earlier resection of a liposarcoma in her thigh. She was noted to have a cautious, steppage gait due again to the left foot drop. According to Mrs. A and her son, she had a history of multiple falls and ordinarily used a brace on her left leg to help with stability. During the course of her hospitalization she had a fall in her hospital room when she tried to go to the bathroom by herself without her brace.

Psychiatrically, she was noted to be extremely anxious and very particular about her personal space in keeping with her OCD diagnosis. Nursing staff noted that she spent significant periods of time ordering and sequencing items in her room. She was additionally found to have a very atypical speech pattern which her primary care physician had noted for at least two years. She offered minimal spontaneous speech but was cooperative with examiners and could follow simple commands without difficulty. Her speech was effortful. She articulately pronounced single words with extreme delay in the initiation followed by marked pauses between words and even when

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pronouncing syllables within individual words. This speech pattern had variously been described in previous records as psychotic (as in thought blocking), aphasic, or intentional/functional. She also had occasional word-finding difficulty.

Mrs. A had a family history of OCD and anxiety disorder in her father, as well as depression in both of her parents. There was also a sister who carried a diagnosis of OCD and according to the family a remarkable history of OCD on the paternal side. The father reportedly expired in his late 60s due to cardiovascular disease and the sister was still living without evidence of dementia. There was no known history of significant early-onset dementia or neurological illness in the family.

## Neuroanatomical Evaluation

As part of her general work-up and evaluation, neuroimaging studies were performed. Initially, computed tomography (CT) with contrast was ordered to rule out an infarct or mass lesion that might explain Mrs. A's speech problems. The CT scans were interpreted as normal although they did incidentally report some degree of left greater than right widening of the Sylvian fissure. A subsequent MRI scan demonstrated subtle asymmetric cortical atrophy with more prominent sulci apparent in the left frontotemporal lobes (Figure 1).

Given the subtleness of the imaging findings and the atypical nature of her language deficit, there remained a great deal of uncertainty as to whether it represented organic dysfunction. Neuropsychological testing was done and demonstrated essentially static cognitive deficits and perhaps some mild improvement over an earlier May 2003 performance (Table 1). There was also very prominent "cognitive splitting" in that she performed considerably better in right hemisphere, visuospatial tasks and considerably worse in left hemisphere, language-related tasks. Language testing was notable for severe impairment of verbal fluency, moderate to severe impairment of naming, and mild impairment of repetition. In contrast to her expressive difficulties, auditory and reading comprehension were close to normal. These language deficits, taken together with her clinical picture and imaging findings, suggested the diagnosis of frontotemporal lobar degeneration (FTLD); the non-fluent progressive aphasia subtype in particular (Neary *et al*., 1998). In an effort to confirm this, she underwent a SPECT perfusion study (Figure 2), which demonstrated prominent left frontal and temporal hypoperfusion consistent with the clinical diagnosis. Despite the mild rotation in the image provided, neuroradiology read it as having hypoperfusion of the basal ganglia.

## Treatment and Follow-up

She was evaluated for ECT and eventually underwent this procedure; however, the team was not able to initiate a seizure. It is not clear why, even with bilateral lead placement at the highest settings permissible, the team was not able to produce a seizure. The inability to produce a seizure is a very rare event and the ECT team theorized that this may have been due to her cortical atrophy. After this, the primary team opted to puruse a more aggressive pharmacological regimen. Her fluvoxamine was rapidly increased to a dose of 250 mg twice daily, and she was also started on dexedrine 5 mg daily. She ultimately improved some with these adjustments in her pharmacotherapy and was discharged to an assisted living facility.

The patient continued to be followed by psychiatry after her discharge but had only one subsequent visit to the neurology service. As her stay at the assisted living facility progressed, she became more bradykinetic and bed-bound, and she was then transferred to a nursing home.

Approximately two years after the hospitalization, the patient expired at the nursing home. A post-mortem was requested by her son in July 2005, and it established a diagnosis of progressive supranuclear palsy (PSP) based on the characteristic distribution of neurofibrillary tangles and neuropil threads in the pons, substantia nigra, subthalamic nucleus,

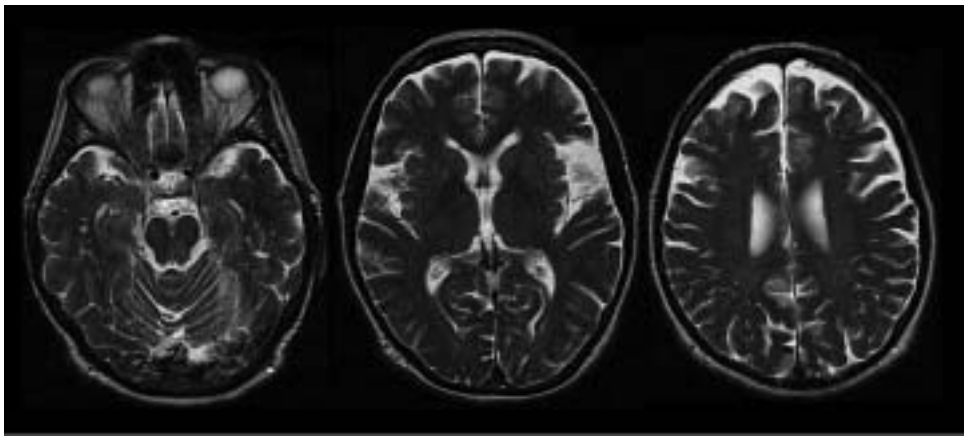

**Fig. 1.** Representative T2-weighted axial MRI scans for Mrs. A showing left greater than right perisylvian atrophy (middle image). Atrophy in the superomedial frontal lobes is relatively symmetric (rightmost image). The left side of the image corresponds to the right side of the brain (radiologic convention).

**Table 1.** Summary of Mrs. A's Neuropsychological testing from May and December 2003

| | May 2003 | | Dec 2003 | |
|---|---|---|---|---|
| Neuropsychological Test | Raw Score | T-Score | Raw Score | T-Score |
| Wechsler Adult Intelligence Scale (WAIS)-III | | | | |
| Information | 7 | 29 | 9 | 37 |
| Digit span | 6 | 30 | 6 | 29 |
| Arithmetic | 4 | 21 | 5 | 25 |
| Similarities | 6 | 24 | 8 | 32 |
| Comprehension | | | 2 | 10 |
| Picture completion | 8 | 37 | 6 | 30 |
| Digit symbol | 3 | 13 | 3 | 13 |
| Block design | 4 | 22 | | |
| Matrix reason | | | 9 | 39 |
| California Verbal Learning Test, short form, learning trials | 21 | 36 | 21 | 36 |
| California Verbal Learning Test, short form, short delay | 8 | 45 | 8 | 45 |
| Boston Naming Test | | | 42 | 28 |
| Aphasia Screening Exam | 16 | 20 | 16 | 20 |
| Peabody Individual Achievement Test Reading Recognition Subtest | 58 | 25 | 66 | 28 |
| Body part identification | | | 20 | 56 |
| Commands | | | 13 | 4 |
| Complex ideational material | | | 9 | 20 |
| Automated sequences | | | 6 | 1 |
| Repeating phrases, high probability | | | 8 | 47 |
| Repeating phrases low probability | | | 7 | 38 |
| Responsive naming | | | 25 | 1 |
| Reading sentences and paragraphs | | | 9 | 44 |
| Animal naming | 4 | 5 | 4 | 5 |
| Greek crosses (Heaton's System) | 3 | 44 | 2 | 56 |
| Grooved peg right hand | | | 155 | 21 |
| Grooved peg left hand | | | 170 | 23 |

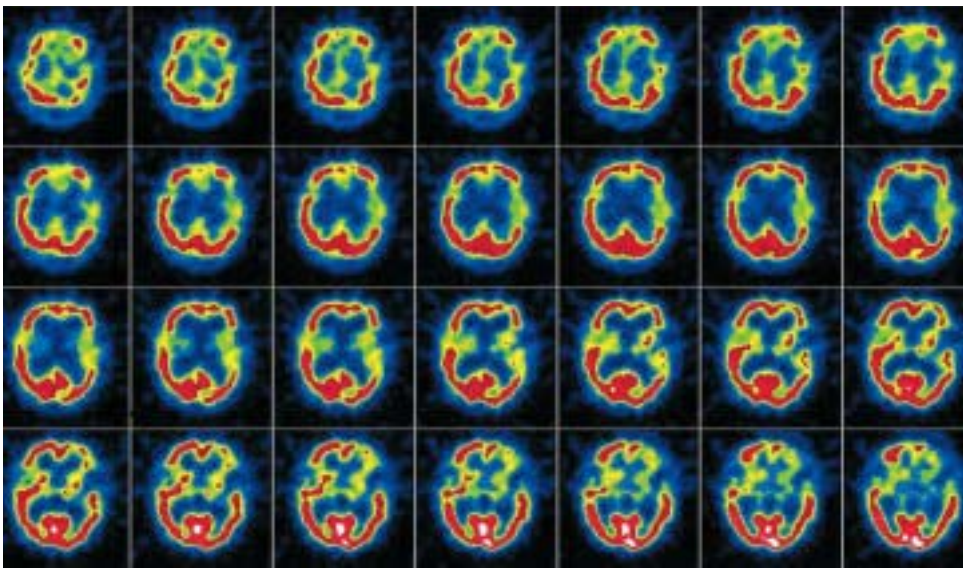

**Fig. 2.** SPECT Scans for Mrs. A showing decreased uptake in the left frontal, left temporal, and caudate regions. The left side of the image corresponds to the right side of the brain.

and striatum associated with widespread presence of abnormal tau-immunoreactive glia (Dickson, 2006).

## Neuropathology

The gross analysis of the brain showed mild diffuse cortical atrophy (1.420 kg). Sequential transverse sectioning revealed a right parietal acute infarction along the middle cerebral artery territory. No further significant gross abnormalities were found in the remaining brain, which showed an unremarkable corpus striatum, thalamus, and other subcortical nuclei; moderately pigmented substantia nigra and locus ceruleus; symmetrical basis pedunculi; normal inferior olives; and symmetrical pyramids.

The microscopic evaluation of the neocortical sections revealed moderate spongiform changes of the superficial cortical layers. Gallyas silver impregnation and Tau immunostaining revealed numerous tufted astrocytes and neuropil threads. Additionally occasional oligodendroglial coiled bodies were seen in the underlying white matter (Figure 3).

Established criteria and techniques for distinguishing neurodegenerative disorders were used in the microscopic neuropathologic studies (Dickson, 2005; Munoz *et al*., 2003). Numerous globose tangles were found in neurons of the substantia nigra, periaqueductal gray matter, locus ceruleus, nucleus basalis of Meynert, caudate, and in the subthalamic and pontine nuclei. These changes were associated with gliosis and neuronal cell loss and, as shown by Gallyas and Tau stains, numerous neuropil threads and occasional tufted astrocytes. The superior colliculi contained numerous neuropil threads, but only rare Tau positive tangles. These typical findings are illustrated in Figures 3 and 4. Ballooned neurons, a finding associated with corticobasal degeneration (Dickson, 1999), were not seen. No Lewy bodies were found in any section.

Beta-amyloid immunostaining and Gallyas silver impregnation demonstrated sparse plaques and rare neurofibrillary tangles in the sampled neocortex, the hippocampal CA1 area, and the entorhinal cortex. Mild atherosclerotic changes were diffusely present; there was no evidence of amyloid angiopathy. A focal area of acute infarction, showing neuronal ischemic changes, frequent axonal spheroids, and reactive astrocytic nuclei, was incidentally found in the right parietal cortex.

## Discussion

This case raises several important points in the diagnosis and management of complex neuropsychiatric dementias. First, FTLD generally and perhaps the NFPA variant more particularly (Josephs *et al*., 2006) frequently shows PSP pathology at autopsy. It is increasingly well-established that FTLD and PSP frequently show prominent clinical and pathological overlap (Kertesz & Munoz, 2004). It is no surprise, therefore, that the neuroimaging would overlap as well. In Mrs. A's clinical presentation, there was initially little to suggest a diagnosis of PSP which was established on final pathological analysis. In support of the diagnosis was a history of onset of symptoms after age 40 which later came to include prominent apathy and speech difficulties. In addition, the patient had gait instability likely secondary to her post-surgical foot-drop

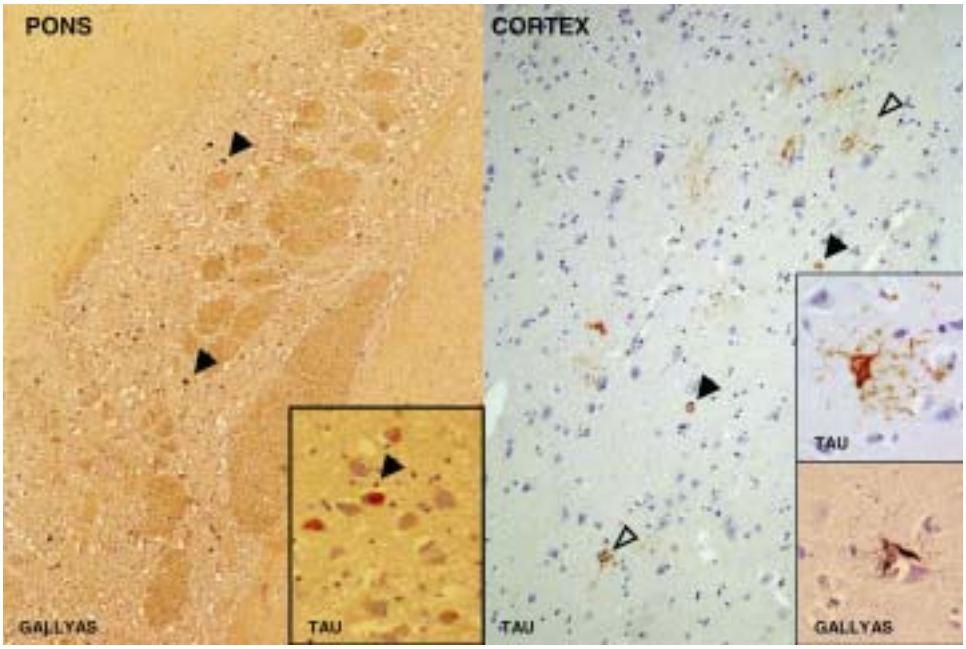


**Fig. 3.** Left panel. Numerous pontine globose tangles are highlighted by Gallyas staining and Tau immunostaining (bottom left inset). Right panel. The sampled frontal cortex shows diffusely scattered Tau-expressing abnormal tufted astrocytes. The insets show the characteristic tufted astrocyte highlighted by a Gallyas and Tau staining. (Arrow: intraneuronal tangle; open arrowhead: tufted astrocyte).

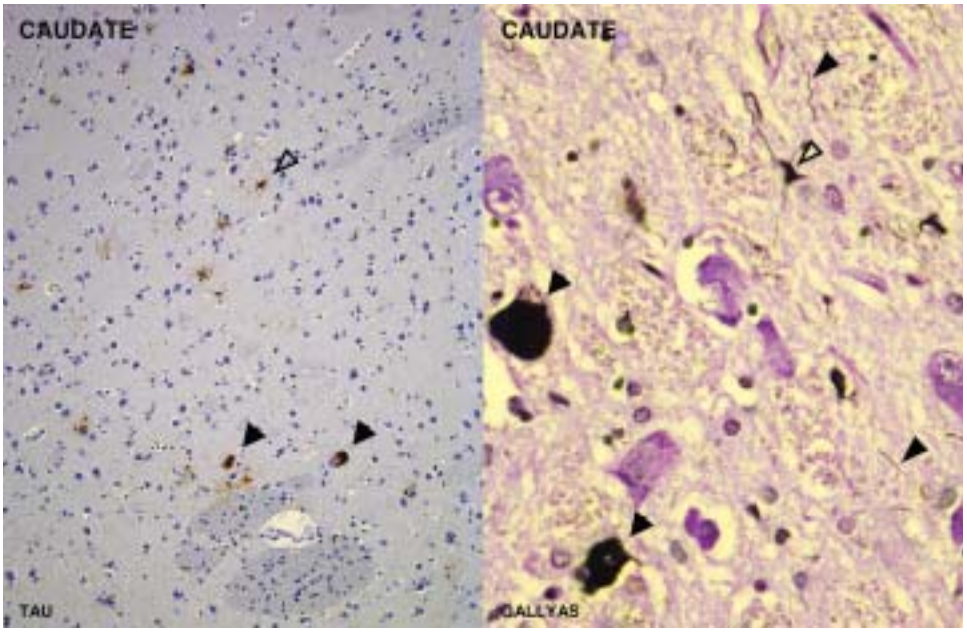


**Fig. 4.** Left panel. Tau immunostaining of the caudate nucleus highlights the numerous intraneuronal globose tangles and the frequent tufted astrocytes. Right panel. A Gallyas stain of the caudate nucleus illustrates the characteristic argyrophilic globose tangle, tufted astrocytes and neuropil threads. (Arrow: intraneuronal tangle; open arrowhead: tufted astrocyte; closed arrowhead: neuropil thread).

but which certainly could have been compounded as her PSP progressed. Mrs. A did not exhibit supranuclear gaze palsy or impaired visual saccades on her neurologic exam.

In one of the largest neuroimaging studies of PSP patients, Macia and colleagues found that in addition to the common symptoms of early falls and gaze problems, prominent atrophy in the frontal, temporal, and parietal regions was a frequent finding (Macia *et al*., 2003). In addition, early and atypical onset of OCD symptoms combined with language difficulties characterized by hypokinetic speech may be further hallmarks of PSP. Josephs and colleagues have suggested that the language disorder in NFPA cases with PSP pathology may reflect speech apraxia rather than the more typical Broca's type aphasia commonly seen in NFPA (Josephs *et al*., 2006). In retrospect, this distinction appears to be an apt one in our case where the patient had prominent difficulty forming vocal sounds even at the sub-syllable level.

Second, Mrs. A showed a progression in her illness from symptoms of OCD in her 40s to depression in her 50s, and then evidence of speech pathology and dementia in her 60s. Assuming that OCD was the first manifestation of her neurodegenerative disorder, this progression highlights the gradual pace with which these disorders may declare themselves and makes the important point that these patients often do not get diagnosed until language is affected. We see Mrs. A as moving across the arc of these diagnoses in a gradual transformation toward PSP. We have outlined the diagnostic criteria that factor into this case in Table 2. When considering these diagnoses, it is important to consider the degree to which some of the criteria overlap which likely result from related pathways that are being affected. Destee and colleagues have previously reported an association of OCD behaviors with PSP (Destee *et al*., 1990). OCD behaviors have also been reported to have associations with a number of other neurologic conditions including Huntington's Disease (Cummings & Cunningham, 1992), basal ganglia lesions (Laplane, 1994), and damage to the caudate nuclei (Penissonbesnier, Legall, & Dubas, 1992). The caudate nuclei in this case were moderately affected with numerous intraneural Tau positive tangles and a moderate neuronal cell loss. We presume that the OCD symptoms were due to damage in the circuits that run through the caudate, thalamus, globus pallidus, and orbitofrontal coretex (Lopez-Ibor, 2003; Saxena & Rauch, 2000). One critical issue and diagnostic clue pertains to the timing of the presentation of OCD. Idiopathic OCD usually begins in adolescence and then has a waxing and waning course over the individual's lifetime whereas the later onset of OCD, as in this case, should raise suspicion for an underlying neurodegenerative disorder (Cummings & Cunningham, 1992).

Third, the predominance of psychiatric and language symptoms in this case and a recent retrospective review of FTLD and PSP cases demonstrate that cortical aspects of PSP can occasionally dominate the clinical presentation with movement difficulties emerging much later in the course. In this case, due to the presence of another illness which affected the patient's gait, it is difficult to assess the degree to which she may have been having additional gait trouble from PSP. During her inpatient admission and on one subsequent neurology clinic visit she was not noted to have difficulty with eye movements or prominent parkinsonism. Given the relatively minimal nature of her movement problems until the

**Table 2.** Major diagnostic criteria for phenomena considered

| Obsessive-Compulsive Disorder (DSM-IV TR 2000) | Frontotemporal Lobar Dementia (FTLD) based on Neary Criteria (Neary *et al*., 1998) | | Progressive Supranuclear Palsy (Litvan *et al*., 1996) |
|---|---|---|---|
| | Frontotemporal Dementia | Non-Fluent Progressive Aphasia | |
| Recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress | Insidious onset and gradual progression | Insidious onset and gradual progression | Possible PSP requires the presence of a gradually progressive disorder with onset at age 40 or later, either vertical supranuclear gaze palsy or both slowing of vertical saccades and prominent postural instability with falls in the first year of onset, as well as no evidence of other diseases that could explain these features. |
| The thoughts, impulses, or images are not simply excessive worries about real-life problems. | Early decline in social interpersonal conduct | Nonfluent spontaneous speech with at least one of the following:agrammatism, phonemic paraphasias, anomia | Probable PSP requires vertical supranuclear gaze palsy, prominent postural instability, and falls in the first year of onset, as well as the other features of possible PSP. |
| The person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action. | Early impairment in regulation of personal conduct | Speech and language (stuttering or oral apraxia, impaired repetition, alexia, agraphia, early preservation of word meaning, late mutism) | Definite PSP requires a history of probable or possible PSP and histopathologic evidence of typical PSP. |
| The person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion) | Early emotional blunting | Behavior (early preservation of social skills, late behavioral changes similar to FTD) | |
| Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly | Early loss of insight | Late contralateral primitive reflexes, akinesia, rigidity, and tremor | |
| The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive. | Behavioral disorder (decline in personal hygiene and grooming, mental rigidity and inflexibility, distractibility and impersistence, hyperorality and dietary changes, perseverative and stereotyped behavior, utilization behavior) | | |
| At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable. | Speech and language (altered speech output, aspontaneioty and economy of speech, stereotypy of speech, echolalia, perseveration, mutism) | | |
| The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships. | Physical signs (primitive reflexes, incontinence, akinesia, rigidity and tremor, low and labile blood pressure) | | |

last year of her life, it seems that the cortical aspects of her illness continued clinically to eclipse the involvement of the basal ganglia and midbrain regions noted at autopsy.

Finally, these findings lead to the conclusion that refractory psychiatric patients should be more closely evaluated for the potential of underlying neurodegenerative processes. In this case, we can identify several refractory processes that suggest a possible common degenerative root cause. First, there is the long-standing OCD which is atypical in its presentation and course. It is clear that OCD and other behavioral problems can precede FTLD by many years. Second, there is evidence of an evolving speech pathology over the two years prior to presentation without evidence of stroke or other explanatory processes. Finally, the refractory nature of her depressive illness in the face of multiple medications and treatments, including ECT, suggests that an organic process was operating against treatment.

## Conclusion

The primary psychiatric presentation of PSP is uncommon and may go unrecognized until a more obvious movement or language disorder develops. Clinicians should be aware of the variable presentation of neurodegenerative disorders and consider these in the differential diagnosis when common psychiatric disorders like OCD present with atypical features. Clearly, more cases of OCD associated with PSP pathology will be needed to better determine if atypical OCD indeed reflects evolving PSP over many years or decades. While no good treatments yet exist for this spectrum of diseases, as treatments emerge, early identification will allow for early intervention which should substantially reduce morbidity and mortality in these patients.

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