A Case of Globular Glial Tauopathy Presenting Clinically as Alzheimer Disease

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We report a rare case of globular glial tauopathy (GGT) in an 80-year-old man presenting clinically with Alzheimer-type dementia. The clinical phenotype was characterized by slowly progressive cognitive decline, followed by minimal parkinsonian signs, but without eye-movement abnormalities, personality changes, or neuropsychological features of frontotemporal dysfunction. Neuropathologic findings comprised abundant phospho-tau-positive globular oligodendrogial inclusions and coiled body—type inclusions in white matter. There was minimal Alzheimer disease (AD) pathology; however, rare neuronal and astrocytic phospho-tau-positive inclusions were present. Gallyas silver staining also highlighted glial inclusions in the section of frontal cortex examined. White matter abnormalities were prominent in most sections examined including the limbic and isocortical brain regions. In spite of prominent white matter changes, associated neurodegeneration in the frontal cortex was minimal; however, the hippocampus and adjacent structures showed moderate neuronal loss. The clinical phenotype of this patient is highly unusual for a disease process that is characterized by prominent frontal white matter involvement.
Classification schemes for neurodegenerative diseases are increasingly focused on underlying pathophysiological mechanisms, specifically the type of misprocessed protein (tauopathies and synucleinopathies), rather than on clinical symptoms associated with the disease. Further categorization is based on the cell type with inclusions (glial vs. neuronal) and the anatomic distribution of the specific histopathologic markers. This can occasionally create problems when the clinical presentation is not predictive of the underlying type or distribution of pathologic changes. Tau-processing abnormalities are a key feature of many neurodegenerative diseases including AD and fronto-temporal lobar degeneration with tauopathy (FTLD-tau), which includes Pick disease, corticobasal degeneration, progressive supranuclear palsy, and the more recently described entity, white matter tauopathy with GGT.\textsuperscript{1–3} Although hereditary FTLD-tau results from specific tau mutations, most tauopathies including GGT are sporadic. The clinical spectrum of GGT is broad but generally includes symptoms of frontotemporal dysfunction and associated features such as Parkinsonism and/or motor neuron disease. We report clinical and neuropathologic findings in an individual with a tauopathy characterized by the presence of globular oligodendrogial inclusions in the white matter. Clinical manifestations were most compatible with AD.

Case History

The patient was an 80-year-old man, originally left-handed, with a consensus diagnosis of AD (AD) who underwent neurological care (J.R.M.) beginning 14 years before death. His initial visit was for vague spells of dizziness and paresthesias of unclear etiology. Mild deficits in memory were noted (MMSE=26/30 with 0/3 delayed recall), but the neurological examination was otherwise normal. Formal neuropsychological testing revealed deficits in delayed free recall but was otherwise intact. He was believed to perhaps have a learning disorder but “… it is not possible to rule out an early stage [of dementia].” Repeat testing 1 year later showed deficits in recall along with new deficits in matrix (visuospatial) and arithmetic reasoning, but the decline overall was slight, and the deficits did not reach the threshold of dementia.

The patient was seen intermittently over the next 4 years, missing several appointments. He continued to have a variety of vague and admittedly mild complaints, including memory loss, lightheadedness, unsteadiness, paresthesias, and sleep attacks. His family confirmed that he was in generally good health but that his memory was getting a little worse. His neurological examination, apart from mild memory deficits (MMSE=27/30, 1/3 on delayed recall), were normal. Laboratory reports, neuroimaging, and a prolonged EEG were also normal.

Repeat neuropsychological testing, 6½ years after initial testing and 7½ years before death, revealed severe deficits in memory with mild deficits in verbal, matrix, and arithmetic reasoning and verbal fluency. Attention and concentration, immediate memory, confrontation naming, and executive functions remained relatively intact. The results were consistent with a generalized dementia. These reports add: “A frontal lobe dementia is not supported given that recent visual and verbal memory performance is poorer than patient’s within normal limits performance on frontal tasks such as foresight and planning.”
The patient’s care was transferred to the Geriatric Research, Education and Clinical Center (GRECC) Memory Loss Clinic and the case was reviewed in a consensus diagnosis conference that included the treating neurologist (J.R.M.), a geropsychiatrist, an internist, and a neuropsychologist. A diagnosis of probable AD was made with no secondary factors contributing to his dementia. Over the next 7 years, the patient's dementia gradually progressed in a pattern consistent with AD. Repeat neuropsychological testing 4½ years before death again revealed generalized dementia with progression in all domains, including executive function. The diagnostic impression was AD. Two years before death, he developed a bilateral pill-rolling tremor, evident while walking, along with decreased arm swing, but no other parkinsonian or other neurological signs emerged. The MMSE was 5/30 6 months before his death, reflecting a decline of about 3 points per year in the last 7 years of his life. The day he died, he was found unresponsive in his nursing home, was brought to the emergency room, and was found to have a markedly elevated cardiac troponin. He was DNR/DNI and died in the emergency room.

Neuropathology Results

Brain autopsy was performed at the request of the next of kin who gave written informed consent. Formalin-fixed tissue was available for examination. Tissue sections were obtained from all lobes of the cerebral cortex and basal ganglia, thalamus, cingulate gyrus, amygdala, hippocampus, midbrain, pons, medulla, and cerebellum. Histopathologic examination of hematoxylin and eosin stained sections was performed on 5-mm thick sections of formalin-fixed, paraffin-embedded brain tissue blocks. Modified Bielschowsky silver stained sections from frontal cortex, hippocampus and amygdala were assessed. Gallyas silver staining was performed on 50 mm formalin fixed floating sections of frontal cortex. Immunostaining was performed for phosphorylated tau (AT8 Mouse Monoclonal 1:3000, 1-h incubation, 1:8000, overnight; Thermo Scientific Pierce), α-synuclein (Mouse Monoclonal 1:10,000 to 1:11,000, 1-h incubation; Covance), and TDP-43 (Rabbit Polyclonal 1:8000, 1-h incubation; Protein Tech Group Inc.)

The brain weighed 1175g, and a gross external examination showed only mild diffuse atrophy. Coronal sections revealed severe hippocampal atrophy. Coalescing lacunar infarcts involving the right caudate, putamen, and the internal capsule (0.6 to 1.5 cm) were present. The ventricular system was severely dilated throughout but most notably at the temporal horns. Microscopic examination of Bielschowsky staining patterns revealed sparse to moderate frontal cortex neuritic plaques in a pattern consistent with the age of the patient, but no mature neurofibrillary tangles were observed. There was significant neuronal loss involving the hippocampus and adjacent structures, including the subiculum, and extending to and including the parahippocampal gyrus. Although TDP-43-positive inclusions were present in the vast majority of cases of hippocampal sclerosis,4 no TDP-43-positive inclusions were present in the hippocampus, amygdala, or frontal cortex. No pathologic changes were identified with α-synuclein staining of the sections of pons, midbrain, deep gray nuclei, or frontal cortex.

The most striking finding on immunohistochemical analysis was of oligodendrogial phospho-tau positivity in the white matter in nearly all sections examined, including the...
frontal and mesial temporal lobes, deep structures, and the brainstem. White matter phospho-tau abnormalities were much less severe in a section of parietal cortex and essentially absent in the occipital cortex. Phosphorylated tau cytoplasmic abnormalities included glial oligodendrogial inclusions and axonal-like profiles, which may represent distended inclusions within oligodendrocytic processes (Fig. 1), and neuronal inclusions, rare astrocytic inclusions, and tau positivity within neuritic plaques in the cortex were also seen. The specific histologic features and the general anatomic distribution (Table 1) were consistent with those described previously for dementia with globular glial inclusions.

Discussion

Diseases characterized by phospho-tau abnormalities range from disorders that exhibit tau pathology in glia alone to those in which the only tau pathology is the neurons.5 Within this spectrum, an overlapping pattern of neuronal and glial abnormalities has been described in cases of CBD (including some presenting clinically with primary progressive aphasia),6,7 in cases with frontotemporal lobar degeneration, in cases with or without parkinsonism and motor neuron disease,8,9 and in cases with striking parietal and focal occipital lobar degeneration.10 On the basis of the similar histo-pathologic findings, it has been proposed that many of these diseases be grouped as frontotemporal degeneration, and a nomenclature for subtypes has been described.11 GGT also falls within the overlapping range of the glial-neuronal spectrum but with a preponderance of white matter involvement that has been described in other pathologically similar cases.12 These and other reports have illustrated the broad clinicopathologic variability of sporadic tauopathies.

This case illustrates the difficulties associated with classifying a disease with a distinct histopathologic appearance but in association with neurodegeneration in a variable range of brain regions. Interestingly, frontotemporal clinical symptoms were not present in the current case in spite of prominent white matter pathology. Recent molecular-based neuropathologic classification schemes, which rely on identifying specific protein abnormalities, highlight the importance of developing methods for assessing biomarkers reflective of the disease category during life. However, even within a specific biochemical category of disease, both the cellular and anatomic distributions of involvement are difficult to predict during life and not necessarily well correlated with clinical presentation. In this case, there may have been 2 entities producing the clinical picture: hippocampal sclerosis with moderate neuronal loss and a diffuse white matter tau-opathy with the white matter loss. The presence of simultaneous pathologies arising in the same brain of elderly subjects is becoming recognized as a major challenge for diagnosis.

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References

Figure 1.
Gallyas, ×40 magnification (A), and phospho-tau (AT8), 20× magnification, staining of the frontal white matter showing glial inclusions and axonal-like phospho-tau-positive profiles (B, C).
### Table 1
Semiquantitative Assessment of the Anatomic Distribution of Key Histopathologic Features

<table>
<thead>
<tr>
<th>GOIs</th>
<th>Frontal Lobe</th>
<th>Hippocampus</th>
<th>Amygdala</th>
<th>Basal Ganglia</th>
<th>Cerebellum</th>
<th>Midbrain</th>
<th>Pons</th>
<th>Medulla</th>
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<tbody>
<tr>
<td>Neuronal tauopathy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
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<td>+</td>
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<tr>
<td>Astrocytic tauopathy</td>
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<td>+</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neuritic plaques (Biel)</td>
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<td>++</td>
<td>++</td>
<td>0</td>
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GOI indicates globular oligodendroglial inclusions.