INTRODUCTION

Frontotemporal lobar degeneration (FTLD) comprises a group of disorders with diverse histopathologic abnormalities that are associated with circumscribed degeneration of the frontal and temporal cortex (1). Patients with FTLD may present with frontotemporal dementia (FTD) characterized by progressive deterioration in behavior, personality, and cognition that is often associated with language dysfunction (2). Some individuals may present with semantic dementia or progressive nonfluent aphasia (3). Parkinsonism or motor neuron disease may also be observed (4). Neuropathologically, these disorders can be associated with abnormal inclusions made of the microtubule-associated protein tau in neurons or in both neurons and glial cells (5). In cases of FTLD with tau-negative, α-synuclein-negative, ubiquitin-positive inclusions, neuronal changes may harbor the TAR DNA-binding protein 43 (TDP-43) (6, 7); in addition, disease forms with α-internexin-positive inclusions or none of these may occur (1). Both sporadic and genetic forms of FTLD have been described. Genetic forms have been found to be associated with mutations in the Microtubule Associated Protein Tau (MAPT) (8–10), Valosin-Containing Protein (11), Charged Multivesicular Body 2B (12), Progranulin genes (13, 14), but not yet in the TDP-43 gene (15–17).

Sporadic tauopathies include Pick disease (PiD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), argyrophilic grain disease (AGD), and neurofibrillary tangle dementia (18). Classification is based on the cellular and anatomical distribution of tau-immunoreactive structures, the ultrastructure of tau filaments, and the isoform profile of pathological tau bands. Two haplotypes (H1/H2) in MAPT, including 2 major ancestral H1 haplotypes, may influence the phenotype (19, 20).

There have been some reports of atypical variants of tauopathies that cannot be classified into known disease categories (21–28). Here, we describe 7 cases with a uniform neuropathologic phenotype characterized by the presence of predominantly white matter globular glial inclusions (GGIs) consisting of 4-repeat (4R) tau, thereby expanding the spectrum of tauopathies.
MATERIALS AND METHODS

Subjects

The archive of the Department of Neuropathology of the National Institute of Psychiatry and Neurology, Budapest, Hungary, consists of approximately 10,000 cases with a wide variety of neuropsychiatric diseases. The present study was initiated by one of the authors (Gabor Kovacs) who examined brain autopsies in this institute between 2003 and 2007. During this period, dementia had been diagnosed in 35% of all autopsied patients (n = 1,129). Among dementia cases, 6% had FTLD. The primary objective was to identify cases for research on FTLD. As a first approach, based on the medical documentation, one of the authors (Katalin Majtenyi) selected cases in which PiD or unclassifiable neurodegenerative disease with frontotemporal atrophy had been diagnosed based on medical documentation and after the neuropathologic examination; current terminology of FTLD had not been defined at this time. Sixty cases from 1966 to 2006 were identified. Using immunohistochemistry for tau and ubiquitin, several anatomical regions from each case were studied; we describe 7 of these cases in the present study. Clinical information on the patients was obtained by retrospective examination of clinical records and for 1 case (Case 6) by interviewing family members. Periods of available clinical documentation of patients ranged between 2 and 10 years. The study was approved by the local ethical committee.

Neuropathology

For all 7 cases, formalin-fixed paraffin-embedded blocks of several brain regions, including frontal, anterior cingulate, temporal, parietal, and occipital cortices, basal ganglia, thalamus, hippocampus, amygdala, brainstem, and cerebellum were available. The spinal cord had been collected from 1 case (Case 7). Seven-micrometer sections were stained using hematoxylin and eosin, Luxol fast blue-periodic acid Schiff (PAS), Congo red, thioflavin S, and modified Bielschowsky and Gallyas silver stains. Immunohistochemistry was carried out using the following antibodies against tau: monoclonal AT8 (1:200; Pierce Biotechnology, Rockford, IL; pS202/pT205), AT100 (pT212/pS214/pT217), AT180 (pT231), AT270 (pT181), HT7 (159-163) (all 1:500, Innogenetics, Antwerp, Belgium), 12E8 (1:500, Elan Pharmaceuticals South San Francisco, CA; pS262/S356), anti-4R tau (RD4; 1:200; Table 1).

### TABLE 1. Summary of Clinical and Genetic Data of 7 Individuals Affected by Frontotemporal Lobar Degeneration With Abundant White Matter Globular Glial Tau Pathology

<table>
<thead>
<tr>
<th>Case</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
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<tbody>
<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
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<td>Age at death, years</td>
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<td>76</td>
<td>78</td>
<td>71</td>
<td>71</td>
<td>81</td>
</tr>
<tr>
<td>Cause of death</td>
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<td>BPN</td>
<td>BPN</td>
<td>BPN</td>
<td>BPN, UREM</td>
<td>BPN</td>
<td>AMI</td>
</tr>
<tr>
<td>Documented disease duration, years</td>
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<td>&gt;5</td>
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<td>&gt;2</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Reason of admission to hospital</td>
<td>Behavioral changes, bulimia, disorientation (lost in city)</td>
<td>Forgetfulness, progressive aphasia</td>
<td>Forgetfulness, progressive aphasia, self neglect, wandering</td>
<td>Withdrawal, behavioral change</td>
<td>Behavioral change, repeated penalty for stealing, lack of cooperation</td>
<td>Acute infarct in RMCA territory</td>
<td>FSHD, anxiety attacks, depression</td>
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<tr>
<td>Withdrawal</td>
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<td>ND</td>
<td>+</td>
<td>+</td>
<td>−</td>
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<td>−</td>
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<td>Remarks</td>
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<td>Transient delirant states, epileptic seizures*</td>
<td>Transient delirant states</td>
<td>Inappropriate laughing, transient anxiety states</td>
<td>Before the admission: withdrawn, change of circadian rhythm</td>
<td>FSHD known for decades (no muscle biopsy)</td>
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</tr>
</tbody>
</table>

*Grand mal seizures.

AMI, acute myocardial infarct; BPN, bronchopneumonia; F, female; FSHD, facio-scapulo-humeral dystrophy; M, male; NA, not available; ND, not documented; PYN, pyelonephritis; RMCA, right middle cerebral artery; UMN, upper motor neuron; UREM, uremia; +, yes; −, no.
Upstate, Charlottesville, VA), and anti-3R tau (RD3; 1:2000; Upstate). Additional monoclonal antibodies used were: anti-β-amyloid (1:100; Novocastra Lab Ltd, Newcastle, United Kingdom), anti-TDP-43 (1:2000, Abnova Corp, Taipei, Taiwan), anti-CD68 (1:1000, Dako, Glostrup, Denmark), anti-HLA-DR (1:100, Dako), anti-myelin proteolipid protein (1:500, Serotec, Kidlington, Oxford, United Kingdom), anti-amyloid precursor protein (1:500, Millipore/Chemicon, Billerica, MA), anti-phosphorylated neurofilament (SMI-31, 1:2500, Covance, Berkeley, CA) and anti-α-synuclein (1:10,000, clone 4D6, Signet, Dedham, MA). The following polyclonal antibodies were used: anti-ubiquitin (1:200, Dako), anti-p62 (guinea pig, 1:4000, Progen Biotechnik GmBh, Heidelberg, Germany), anti-glial fibrillary acidic protein (GFAP; Dako), anti-trypsin (1:400, Dako), and anti-phosphorylated neurofilament 200 (SMI-200, Covance).

FIGURE 1. Macroscopic overview of representative brains. Note the prominent frontotemporal atrophy in Case 1 (A, B) and the asymmetric atrophy (left > right) in Case 3 (C, D). Scanned original photographs from 1966 (Case 1) and 1975 (Case 3).

| Table 2. Summary of Neuropathologic Alterations of 7 Individuals Affected by Frontotemporal Lobar Degeneration in Addition to Abundant White Matter Globular Glial Tau Immunoreactivity |
|------------------------|--------|--------|--------|--------|--------|--------|--------|
| Case/Neuropathologic Changes | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 |
| Brain weight, g | 1,000 | 1,220 | 1,000 | 1,150 | 960 | 1,150 | 1,300 |
| Frontotemporal atrophy | + | + | + | + | + | + | + |
| Superficial spongiosis | + | + | + | + | + | + | + |
| Ballooned neurons | + | + | + | + | + | + | + |
| Non-argyrophilic Tau IR grains | + | + | + | + | + | + | + |
| Spheric neuronal cytoplasmic inclusions | + | + | + | + | + | + | + |
| Occasional tufted astrocytes | + | + | + | + | + | + | + |
| Diffuse neuronal cytoplasmic Tau IR | + | + | + | + | + | + | + |
| Neuritic plaques | – | – | Sparse | Sparse | – | Moderate | – |
| Neurofibrillary tangles (Braak stage) (34) | – | – | + (II) | + (II) | – | + (III) | + (II) |
| Brain infarct | – | – | – | + (T) | + (L) | + (T) | – |

IR, immunoreactivity; L, lacunar in basal ganglia; T, territorial (medial cerebral artery).+, present; –, absent.
protein (1:3000, Dako), anti-myelin basic protein (1:200, Dako), anti-TDP-43 (1:100, ProteinTech Group, Chicago, IL), and anti-α-B-crystallin (1:500, Novocastra). As a secondary detection system, the Envision kit (Dako) was used with diaminobenzidine as the chromogen.

Genetics

Genomic DNA was extracted from blood (in Cases 6 and 7) and formalin-fixed paraffin-embedded brain tissue (in Cases 1–4) using standard protocols (29). Analysis of the MAPT exons and flanking intronic regions was carried out as described (10). Standard amplification reactions were done using 50 ng of genomic DNA and examined by agarose gel electrophoresis. The amplification reactions were treated with ExoSap-IT (USB, Cleveland, OH) to remove unincorporated primers and nucleotides. Asymmetric amplification using the DTCS quick start kit (Beckman Coulter, Fullerton, CA) was performed, and the products were loaded onto a CEQ 8000 GeXP Genetic Analysis System (Beckman Coulter). DNA sequences were compared with the published MAPT sequence (www.ncib.nlm.nih.gov). The haplotype status was determined by examining the sequences in which the polymorphisms resided. For the DNA extracted from formalin-fixed paraffin-embedded tissue, haplotypes were determined by assessing single nucleotide polymorphisms in Exons 1 and 9 using previously described primers (30). Amplification products were digested with AluI (exon 1) or MspI (exon 9) and analyzed on a 2% agarose gel. ApoE genotyping was performed as described (31).

Biochemistry

Frozen tissue samples of amygdala and hippocampus (with subiculum and hippocampal white matter) from Case 7 were used for sarkosyl extraction, as described (32). Sarkosyl-insoluble material was run on 10% Tris/glycine gels and blotted onto polyvinylidene fluoride membranes. The blots were incubated with anti-tau antibodies 133 (against the amino-terminus, 1:1000), 134 (against the carboxy-terminus, 1:5000), AT8 (1:1000), or PS422 (pS422, 1:500) for 1 hour at room temperature and developed using enhanced chemiluminescence (GE Healthcare).

Electron Microscopy

For ultrastructural analysis of inclusions, small samples of affected temporal white matter obtained by needle biopsy from the paraffin block of Case 6 were deparaffinized, fixed in glutaraldehyde, and embedded in epoxy resin. Ultrathin sections of 80 to 90 nm were analyzed with a Zeiss electron microscope. Aliquots of the sarkosyl-insoluble dispersed filament preparations from amygdala and hippocampus of Case 7 were processed for immunoelectron microscopy, as described (33). Micrographs were recorded on a Philips EM208S microscope at a nominal...
magnification of 40,000×. Antibodies 134, AT100, and PS422 were used at 1:100.

RESULTS
Summary of Clinical Data
Age at death of the 7 individuals investigated here ranged from 63 to 81 years (mean, 76 years). Social withdrawal was reported in 4 individuals, anxiety and early forgetfulness in 5, and disorientation in 4 (Table 1). Behavioral changes were noted in 6 cases and speech disorder in 4. Alterations in circadian rhythm were present in 2 individuals and hyperphagia in 1. In addition to dementia (5 cases), rigidity (2 cases), upper motor neuron symptoms (4 cases), some in the form of supranuclear facial palsy (2 cases), bilateral Babinski sign (1 case), and hemiparesis (1 case), were also observed in advanced stages. Akinetic mutism was described in 2 individuals. Neither corticobasal syndrome nor gaze palsy was observed. Overall, clinical features were compatible with the frontal variant of FTD.
Neuropathology

Histopathology and Immunohistochemistry

All brains studied showed frontaltemporal atrophy. It was mild in Case 7, moderate in Case 6, and severe in Cases 1 to 5 (Figs. 1A, B). The atrophy was asymmetric (left > right) in Cases 2, 3, and 4 (Figs. 1c, d). Lacunat Case 5) and territorial (Cases 4 and 6) infarcts were also observed. Common histopathologic features (Table 2) comprised spongiosis in the superficial layers of the frontal cortex (Fig. 2A), neuronal cell loss (Fig. 2B), and ballooned neurons, showing diffuse cytoplasmic immunoreactivity for α-B-crystallin in frontal cortex, anterior cingulate cortex, and amygdala (not shown). Reduction of myelin and, less extensively, axons, along with microglial activation, correlated with the severity of white matter tau pathology (Figs. 2C–M). In severely affected areas, macrophages were present (Fig. 2N). Amyloid precursor protein-immunoreactive axonal swellings (Fig. 2J, inset) were rare. Alterations in myelin staining were demonstrated in a hemispheric section (Fig. 3). Early-stage neurofibrillary degeneration (Braak Stage II in 3 cases and Braak Stage III in 1 case) (34), diffuse β-amyloid-immunoreactive, and sparse argyrophilic neuritic plaques were also seen (Table 2); however, none of these cases fulfilled neuropathologic criteria for definite Alzheimer disease (35). Argyrophilic grains were detected in the transentorhinal region in Case 6. The TDP-43- and amyloid-immunoreactive, and sparse argyrophilic neuritic plaques were also seen (Table 2); however, none of these cases fulfilled neuropathologic criteria for definite Alzheimer disease (35). Argyrophilic grains were detected in the transentorhinal region in Case 6. The TDP-43-immunoreactive pathological changes were absent, but granular immunostaining of nuclei was noted. A few α-synuclein-immunoreactive Lewy bodies were observed in the substantia nigra of Case 7.

Immunohistochemistry for Tau

The most prominent alteration was the presence of abundant tau-immunoreactive GGI s, along with non-argyrophilic grains and a few argyrophilic threads, predominantly in white matter (Fig. 4A). Fewer GGI s were present in gray matter (Fig. 4B). Typical oligodendroglial coiled bodies were only rarely observed. Astrocytes in gray matter were immunoreactive for antibody RD4. Gray matter astrocytes showed prominent non-argyrophilic dotlike immunopositivity in the proximal segments of branching processes, with a starlike appearance, reminiscent of tufted astrocytes; thus, they are called tufted-like astrocytes (Fig. 4C). Typical argyrophilic tufted astrocytes as seen in progressive supranuclear palsy were only rarely observed. Pretangle-type staining (Fig. 4D) and occasional spherical cytoplasmic inclusions immunoreactive for RD4 but not RD3 were observed in neurons (Fig. 4E). Anti-RD3 immunolabeled occasional neurofibrillary tangles and sparse neuropil threads. Globose neurofibrillary tangles and astrocytic plaques were not present.

Characterization of GGI s

The diameter of GGI s ranged between 8 and 20 μm (usually 1.5–3.0 times larger than oligodendroglial nuclei). They were closely associated with oligodendroglial and some astroglial nuclei. Their shape was mainly globular, but half-moon and conical shapes were also noted. Globular glial inclusions could be identified using hematoxylin and eosin staining but were much more evident with tau immunostaining. They are argyrophilic, and although the Gallyas method yielded superior results, they could be detected with other silver impregnation techniques, including Bielschowsky; they were ubiquitin immunoreactive and positive for p62. Globular glial inclusions were strongly 4R tau-immunoreactive and could also be stained using a panel of phosphorylation-dependent anti-tau antibodies. Antibody HT7 gave only weak staining. These results are illustrated in Figure 5. By electron microscopy, GGI s comprised granular material and haphazardly oriented filaments of 8 to 9 nm in diameter (Fig. 6).

Anatomical Distribution

Neuronal loss was observed in the frontal, temporal, and anterior cingulate cortices, amygdala, and in particular, the subcortical (Table 3; Figs. 4F–K). The basal nucleus of Meynert and the basal ganglia were only mildly affected; there was some nerve cell loss in the substantia nigra (Fig. 4L). No significant nerve cell loss was present in the subthalamic nucleus.

Tau pathology was more widespread than nerve cell loss (Table 3). Although spherical cytoplasmic neuronal

FIGURE 4. Tau-immunoreactive structures and anatomical distribution of neuropathologic changes in individuals with frontaltemporal lobar degeneration associated with tau-immunonegative globular glial inclusions. The most prominent alteration is the presence of globular glial tau immunoreactivity, together with grainlike structures, predominantly in white matter (A) and, to a lesser extent, also in gray matter (B). Abundant ramified astrocytes (C) showing immunoreactivity with antibody RD4 (right upper inset) are observed in gray matter (Fig. 4A). Fewer GGI s were present in gray matter (Fig. 4B). Typical oligodendroglial coiled bodies were only rarely observed. Astrocytes in gray matter were immunoreactive for antibody RD4. Gray matter astrocytes showed prominent non-argyrophilic dotlike immunopositiv
inclusions were restricted to the frontal and temporal cortices as well as the hippocampal CA1 subregion, pretangles were observed in most regions investigated, including the dentate gyrus, the substantia nigra, the amygdala, the basal ganglia, the thalamus, and many brainstem nuclei (Figs. 4M–O). The spinal cord of Case 7 was devoid of tau pathology. Globular glial inclusions were numerous in periamygdaloid, perihippocampal, and frontal white matter (Table 3). Differences in the numbers of GGIs were noted between cases without overt dementia (Case 7) compared with those with prominent clinical symptoms (Cases 1–5; Figs. 4P–S). Additional brain areas such as the occipital white matter were affected in cases with dementia.

Accumulation of GGIs was prominent at the cortical-white matter junctions (Fig. 4T). The internal capsule (mainly its anterior part), the cerebral peduncle (mainly its medial segment), the descending tracts of the pontine basis (mainly their upper segments), the corpus callosum, the anterior commissure, and the thalamic fascicles consistently showed GGIs (Figs. 4U–X). They were infrequent in the medullary pyramid and absent from the oculomotor and hypoglossal cranial nerves and the optic chiasm. In the 2 individuals who did not exhibit overt dementia (Cases 6 and 7), GGIs were observed mainly in the amygdala and in the hippocampal and frontobasal white matter; they were sparse in the interconnecting tracts. Tufted-like astrocytes were present mainly in frontal, cingulate, and temporal cortices, as well as in amygdala, basal ganglia, and thalamus (Table 3).

Summary of the Neuropathologic Findings

The following features were characteristic: 1) Neuronal loss predominantly in frontal and temporal cortices, subiculum, and amygdala. 2) Prominent involvement of the surrounding white matter with abundant globular, glia-associated, phospho-tau, and 4R tau-immunoreactive inclusions (GGIs) composed of abnormal filaments. Less severe but consistent involvement of the interconnecting (corpus callosum, anterior commissure) and frontopontine tracts, with only mildly affected corticospinal tracts. 3) Correlation of the severity of white matter tau pathology with a reduction in myelin and axonal density, accompanied by

FIGURE 5. Characterization of globular glial inclusions. Hematoxylin and eosin (A), periodic acid Schiff (B), Gallyas (C), Bielschowsky (D, Biel), and thioflavin (E, Thiofl) stains and immunohistochemistry for p62 (F), ubiquitin (G, Ubiq), neurofilament-SMI-31 (H), Tau-AT8 (I), Tau-AT100 (J), Tau-AT180 (K), Tau-AT270 (L), Tau-12E8 (M), Tau-HT7 (N), Tau-RD4 (O), and Tau-RD3 (P). Scale bars = (A–H) 10 μm; (I–P) 100 μm.
microglial activation. 4) Presence of phospho-tau and 4R tau-immunoreactive neuronal cytoplasmic spherical inclusions and pretangles. 5) Dotlike phospho-tau and 4R tau-immunoreactivity in astrocytic processes (tufted-like astrocytes) and a few argyrophilic tufted astrocytes.

**Biochemistry and Electron Microscopy**

Sarkosyl-insoluble tau was prepared from the amygdala and hippocampal formation of Case 7. By immunoelectron microscopy, tau filaments were Alzheimer-type paired helical and straight filaments (PHFs and SFs; Fig. 7a). They were decorated with anti-tau antibodies 134, AT100, and PS422. By Western blotting of sarkosyl-insoluble tau, phosphorylation-independent (133 and 134) and phosphorylation-dependent anti-tau antibodies identified 2 major pathological tau bands of 64 and 68 kd, with a minor tau band of 72 kd being visible in the amygdala sample (Fig. 7B).

**Genetic Analysis**

No mutations were found in the exons and adjoining intronic regions of \( MAPT \) in Cases 6 and 7. The H1/H1 genotype was found in 4 cases (Cases 1, 4, 6, and 7). Cases 2 and 3 could not be analyzed because of the poor quality of the DNA extracted from paraffin-embedded tissue. The \( ApoE \) \( e3/e3 \) genotype was observed in 6 samples (Table 1).

**DISCUSSION**

We report 7 cases with the behavioral variant of FTD and a uniform and distinct neuropathologic phenotype.
characterized by the presence of predominantly white matter GGIs composed of 4R tau. The neuropathologic features, in particular the presence of GGIs, the anatomical pattern of neuronal loss including the sparing of basal ganglia, subthalamic nucleus, and brainstem nuclei, the lack of globose tangles, astrocytic plaques, and argyrophilic grains, as well as the rarity of oligodendroglial coiled bodies and threadlike tau immunoreactivity do not fit into current morphological criteria for sporadic 4R tauopathies such as AGD, CBD, and PSP (36). Lack of 3R immunoreactivity in GGIs and in spherical cytoplasmic neuronal inclusions and the presence of 64 and 68 kd bands by Western blotting distinguish our cases from PiD (37, 38). Based on the presence of GGIs, our cases are also distinct from atypical dementia complex of Guam are also different (39). They are composed of 4R tau but are smaller (3–6 μm) than GGIs and permeated by round structures of 20 to 30 nm diameter (40). So-called oligodendroglial microtubular masses have been described in PiD; however, unlike GGIs, they are glial inclusions that are curved and threadlike (41).

By immunoelectron microscopy, sarkosyl-insoluble tau from Case 7 contained Alzheimer-type PHFs and SFs, despite the presence of major 64 and 68 kd pathological tau bands by Western blotting in the same sample. It is well established that the presence of the latter is indicative of 4R tau (18), in agreement with the immunohistochemical findings. In contrast, PHFs and SFs in Alzheimer disease are made of both 3R and 4R tau (32, 42). Therefore, the present findings extend the morphological spectrum of filaments made of 4R tau.

In 2001, Bigio et al (21) reported a case of a sporadic multiple system 4R tauopathy with dementia. They described dense GGIs in the white matter and lower cortex with similar staining properties to those described herein. These structures also contained filaments with a diameter of 9 to 10 nm. Interestingly, the authors also observed PHF-like filaments in addition to the straight filaments in their ultrastructural evaluation of oligodendroglial inclusions. The density of those inclusions, however, was much lower than in our cases. In 2003, Powers et al (24) described a sporadic case of white matter-dominant tauopathy. There, the extent of pathology, staining properties, and ultrastructural characteristics of the inclusions described were comparable to those in our cases. In contrast to our results, however, the inclusions were negative with antibody 12E8. Powers et al (24) also noted a correlation between the number of glial inclusions and white matter damage. In the same year, Ferrer et al (25) reported a case with primary progressive aphasia. Similar to our case and that of Powers et al (24), FTLD and a reduction in white matter volume were described. The GGI-like structures with comparable staining properties, including phosphorylation of S262 in tau and a Western blot pattern of 2 pathological tau bands of 64 and 68 kd, were demonstrated. The reportedly mainly astrocytic, tau-immunoreactive globules observed in the white matter by Berry et al (22) in a case of progressive aphasia were also reminiscent of GGIs. A comparison of all these case reports with our observations is summarized in Table 4. Although there is some difference between the described details (e.g. on astrocytic tau pathology) or examinations performed, there is considerable agreement among these studies. In addition, in 1998, Molina et al (43) described unusual argyrophilic and phospho-tau immunopositive glial inclusions in a temporal lobe biopsy specimen from a patient with progressive aphasia. They demonstrated perinuclear ring- or sickle-shaped glial inclusions, as well as small tau-immunoreactive globules.

The clinical symptoms in our cases were compatible with a diagnosis of the frontal lobe variant of FTD (2). Withdrawal and akinetic mutism reflected the involvement of anterior cingulate/medial frontal lobe, whereas development of speech dysfunction indicated the spread of neuronal loss to lateral frontal and insular cortices. In other individuals, orbitobasal (ventromedial) frontal lobe dysfunction dominated, including disinhibition and socially inappropriate
behavior (2). In the aforementioned case reports with inclusions resembling GGI-T, similar clinical features, including anxiety, hyperphagia, memory decline, and aphasia, were reported (21, 22, 24, 25, 43). The lack of gaze palsy, corticobasal syndrome, or prominent Parkinsonism was notable.

Josephs et al (44) recently reported 12 cases of atypical PSP with corticospinal tract degeneration, showing symptoms of motor neuron disease with extrapyramidal features. Neuropathologically, these cases exhibited numerous GGI-T in the white matter. We also noted GGI-T in the internal capsule, cerebral peduncle, descending tracts in the pontine base, and to a lesser degree, in corticospinal fibers including the medullary pyramids. Caution is needed in interpreting the less prominent upper motor neuron symptoms in our cases because of the retrospective analysis of archived material and the presence of brain infarcts. Together with the previous case reports, our observations suggest the existence of a spectrum of clinical syndromes associated with the presence of mainly white matter GGI-T. It comprises the behavioral variant of FTD, progressive nonfluent aphasia, and upper motor neuron disease with extrapyramidal features. Whether yet unknown genetic or epigenetic factors may contribute to the observed differences in anatomical distribution and severity merit further studies. The present study is not an epidemiological study, and thus the exact incidence of this disorder cannot be defined. The cases represent a rare form of FTLD and may be found when archival cases with the diagnosis of PiD or unclassifiable tauopathy are re-evaluated.

In our cohort, Cases 1 to 5 had been conventionally diagnosed as PiD based on the presence of ballooned neurons and occasional globular cytoplasmic neuronal inclusions, spongiosis of the superficial layers in the frontal region, and prominent frontotemporal atrophy. Cases 6 and 7 had been evaluated using immunohistochemistry and had been diagnosed as unclassifiable tauopathy with GGI-T.

In our series, overt dementia was absent in 2 cases: 1 patient died of an ischemic stroke (Case 6) and one of a myocardial infarct (Case 7). Because these patients exhibited forgetfulness and some behavioral alterations, however, it is tempting to speculate that their distribution of GGI-T represents brain regions that are affected early in the course of the disease, including the white matter in medial frontal and frontobasal lobes, hippocampal formation, and amygdala. Nerve cell loss was extensive in subiculum and amygdala. In cases with more prominent clinical symptoms and dementia,

TABLE 4. Pathological, Biochemical, and Clinical Features of Sporadic GGI-T in the Present and Previous Reports

<table>
<thead>
<tr>
<th>Feature/Disease</th>
<th>GGI-T</th>
<th>sMST</th>
<th>sFTD</th>
<th>LWMT</th>
<th>sMST</th>
<th>PSP and CSD</th>
<th>CBD</th>
<th>PSP</th>
<th>AGD</th>
<th>PiD</th>
</tr>
</thead>
<tbody>
<tr>
<td>GGI</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No. cases</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>12</td>
<td>Many</td>
<td>Many</td>
<td>Many</td>
<td>Many</td>
</tr>
<tr>
<td>GGI/localization</td>
<td>OG &gt; AS</td>
<td>AS</td>
<td>OG &gt; AS</td>
<td>OG</td>
<td>OG</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>OG</td>
</tr>
<tr>
<td>GGI/size (μm)</td>
<td>8–20</td>
<td>6–10</td>
<td>~6</td>
<td>8–10</td>
<td>6–8</td>
<td>NA</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Coiled bodies</td>
<td>Yes/rare</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>Yes/rare</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Astrocytic tau</td>
<td>Tufted-like (dotlinke in branches)</td>
<td>Tufted-like</td>
<td>Globules in the cytoplasm</td>
<td>Thorny</td>
<td>NA</td>
<td>Tufted</td>
<td>Plaque</td>
<td>Tufted</td>
<td>Branched</td>
<td>Ramified</td>
</tr>
<tr>
<td>H1/H2 haplotype</td>
<td>H1/H1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Filaments</td>
<td>HI/H1</td>
<td>HI/H1</td>
<td>HI/H2</td>
</tr>
<tr>
<td>GGI/Ultrastructure</td>
<td>Haphazardly oriented SF</td>
<td>Dense SF aggregates, PHF-like filaments, fingerprint-like bodies</td>
<td>Dense SF aggregates</td>
<td>Haphazardly oriented SF</td>
<td>HI/H1</td>
<td>HI/H1</td>
<td>HI/H1</td>
<td>HI/H1</td>
<td>HI/H1</td>
<td>NA</td>
</tr>
<tr>
<td>Tau F/Ultrastructure</td>
<td>SF, PHF</td>
<td>SF: 9–10 Rare SF and PHF-like: 20–30</td>
<td>NA</td>
<td>15–8</td>
<td>SF</td>
<td>TR</td>
<td>SF</td>
<td>SF</td>
<td>SF</td>
<td>SF</td>
</tr>
<tr>
<td>Glia filaments/ diameter. nm</td>
<td>8–9</td>
<td>NA</td>
<td>SF: 9–10 Rare SF and PHF-like: 20–30</td>
<td>10</td>
<td>15–25</td>
<td>13–28</td>
<td>10–13</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau blot (kd)</td>
<td>64, 68</td>
<td>64, 68</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>64, 68</td>
<td>64, 68</td>
<td>64, 68</td>
<td>64, 68</td>
<td>60–64</td>
</tr>
<tr>
<td>3R/4R tau isoforms</td>
<td>4R</td>
<td>4R</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4R</td>
<td>4R</td>
<td>4R</td>
<td>3R &gt; 4R</td>
<td></td>
</tr>
<tr>
<td>Clinical phenotype</td>
<td>FLS, SpD</td>
<td>FLS</td>
<td>FLS</td>
<td>SpD, PS</td>
<td>UMN, EP</td>
<td>CBS, PS,</td>
<td>PS, EMD,</td>
<td>FLS</td>
<td>FLS, SpD</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Present cases</td>
<td>(21)</td>
<td>(22)</td>
<td>(24)</td>
<td>(25)</td>
<td>(44)</td>
<td>(36)</td>
<td>(36)</td>
<td>(36)</td>
<td></td>
</tr>
</tbody>
</table>

Comparison of pathology, ultrastructure, biochemistry, and clinical phenotype in sporadic tauopathy with globular glial inclusions (GGI-T) of this series and earlier single case reports reporting GGI-T (sporadic multiple system tauopathy [sMST], sporadic frontotemporal dementia [sFTD], leukoencephalopathy with white matter tauopathy [LWMT]), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) with corticobasal degeneration (CBD), argyrophilic grain disease (AGD), and frontotemporal lobar degeneration with Pick bodies (PiD).

AS, astrocyte; CBS, corticobasal syndrome; EMD, eye movement disorder; EP, extrapyramidal features; F, filament; FLS, frontal lobe symptoms; NA, data not available; OG, oligodendroglial; PHF, paired helical filaments; PS, Parkinson syndrome; SF, straight filament; SpD, speech disorder; TF, Twisted filament; TR, Twisted ribbon; UMN, upper motor neuron symptoms.

*Rare spherical inclusions in glial cells are also reported (36).
the number of GGIIs increased in the aforementioned areas, in parallel with spread to interconnecting and descending white matter tracts and, to a lesser degree, posterior lobe regions.

Our cases with sporadic tauopathy were homozygous for the H1 MAPT haplotype and the ApoE ε3 allele. Homozygosity of H1 predisposes to PSP and CBD, but does not influence the biochemical or neuropathologic phenotype of PSP (45). Current evidence indicates that the ApoE genotype is not a significant risk factor for FTLD associated with pathologic tau (1).

The strength of the present study lies in its systematic and comprehensive neuropathologic evaluation of a small case series. It is limited by the retrospective nature of clinical data collection and the lack of neuroradiological documentation. It remains to be seen whether the reduction in myelin and axonal density (Figs. 2, 3) that characterizes disorders with GGIIs (24, 25, 44) gives rise to a specific signature on neuroimaging. Some of the neuropathologic features reported here are reminiscent of multiple system atrophy (MSA). Thus, the morphology of hyperphosphorylated tau immunopositive GGIIs resembles α-synuclein immunoreactive Pappen-bots bodies (also known as glial cytoplasmic inclusions) (46). Furthermore, MSA is characterized by the loss of myelin, in conjunction with microglial cell activation (47). In addition, cases of MSA where frontal and temporal lobes were mostly affected have been described (48–50). However, unlike the cases described here, MSA is a synucleinopathy with the abnormal filamentous inclusions being made of α-synuclein (51, 52). Therefore, the tauopathy with GGIls extends the group of neurodegenerative disorders in which oligodendriogial pathology predominates beyond the synucleinopathy MSA. Similar to cases of MSA with minimal change (53), our least affected cases also showed more abundant white matter GGIIs than nerve cell loss in affected areas.

In summary, in conjunction with case reports from the literature (21, 24, 25, 44), the 7 cases detailed here indicate that the sporadic tauopathy with GGIIs is a distinct neuropathologic entity associated with sporadic FTLD. Clinically, it is associated with a spectrum of clinical syndromes, including FTD and corticospinal degeneration.

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REFERENCES


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