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Neuroimaging

Expanding the phenotypic associations of globular glial tau subtypes

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Abstract

Introduction: Clinicopathologic correlation in non-Alzheimer's tauopathies is variable, despite refinement of pathologic diagnostic criteria. In the present study, the clinical and neuroimaging characteristics of globular glial tauopathy (GGT) were examined to determine whether subtyping according to consensus guidelines improves clinicopathologic correlation.

Methods: Confirmed GGT cases (n = 11) were identified from 181 frontotemporal tauopathy cases. Clinical and neuroimaging details were collected, and cases sub-typed according to the consensus criteria for GGT diagnosis. Relationships between clinical syndrome and GGT subtype were investigated.

Results: In total, 11 patients (seven males, four females, mean age = 67.3 +/- 10.6 years) with GGT were included. Most, but not all, presented with behavioral variant frontotemporal dementia, but none had amyotrophic lateral sclerosis. Subtyping of GGT proved to be difficult and did not improve clinicopathologic correlation.

Discussion: Sub-classification of GGT pathology may be difficult and did not improve clinicopathologic correlation. Better biomarkers of tau pathology are needed.

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Keywords:

Frontotemporal dementia; Globular glial tau; Tauopathy; Clinicopathological correlation

1. Introduction

A new dawn of therapeutics in neurodegenerative dementia beckons. Agents are being developed to specifically target molecular pathologies such as β -amyloid [1–3], α -synuclein [4], and tau [5]. While encouraging, these developments pose a significant challenge for clinicians trying to influence the course of disease in individual patients. In particular, pathologies causing neurodegeneration develop decades before the onset of symptoms [6,7], meaning that early identification of specific disease processes will be necessary to delay or prevent the progression of neurodegeneration. The ability to select appropriate therapeutic targets, at the right stage of illness, will be required before effective treatments can be implemented.

Although the underlying pathology can be reliably predicted in some clinical dementia syndromes [8–11], clinicopathologic correlation remains a challenge in many others [9,11–16]. For example, TDP-43 and tau pathologies each account for about half of behavioral frontotemporal dementia (bvFTD) cases but have very similar clinical presentations. Furthermore, the non-Alzheimer's tauopathies—diseases associated with the accumulation of phosphorylated tau inclusions without the presence of β -amyloid plaques—have been associated with a wide range of different clinical phenotypes that include variable combinations of cognitive, behavioral, and motor impairments [17]. Could more specific pathologic classification of non-Alzheimer's tauopathies improve clinicopathologic correlation in bvFTD and other forms of frontotemporal dementia, leading to more accurate *in vivo* diagnoses?

The pathologic classification of non-Alzheimer's tauopathies has been revised extensively over recent years, based

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on a number of different characteristics including the biochemical composition of inclusions containing three-repeat (3R) and/or four-repeat (4R) tau, as well as the morphology and the distribution of tau-immunopositive inclusions in neurons and glia [18]. Several distinct pathologic entities are now recognized, but understanding of the relationships between clinical diagnosis and prognosis remains limited [9].

One recently described non-Alzheimer's tauopathy is globular glial tauopathy (GGT), which is distinguished by the accumulation of 4R tau in oligodendroglia and astrocytes, in addition to deposition in cortical neurones [19,20]. The distribution of tau inclusions has prompted the development of a pathologic classification scheme that proposes three pathologic subtypes of GGT [21]. Type I involves the prefrontal and temporal cortices; type II involves both the motor cortex and the corticospinal tracts; type III is defined by the involvement of the prefrontal, temporal, and motor cortices, and the corticospinal tracts [21]. All three subtypes are associated with prominent white matter degeneration. Although the pathologic criteria acknowledge a wide variety of clinical diagnoses in patients with GGT, a more specific relationship between the GGT subtype and clinical features is proposed. For example, type I cases are expected to present with frontotemporal dementia (FTD); type II cases are expected to present with motor neuron disease (MND) and extrapyramidal deficits (i.e., parkinsonism); and type III cases are expected to present with FTD combined with MND and parkinsonism. Such a close clinicopathologic correlation between pathologic GGT subtype and clinical features remains to be proven.

The present study explored three hypotheses; first, can GGT cases be easily pathologically sub-typed according to the scheme outlined in the proposed consensus criteria? Second, is each pathologic GGT subtype associated with any unique clinical, neuropsychological, or neuroradiologic characteristics that might predict GGT pathology when patients are assessed in life? Finally, does subtyping of GGT pathology improve clinicopathologic correlation?

2. Methods

2.1. Participants

Neuropathologically confirmed GGT cases ($n = 11$) were identified from 181 cases with frontotemporal lobar degeneration with tau-immunopositive inclusions (FTLD-tau) held by the Sydney and Cambridge Brain Banks for inclusion in this study. Both brain banks hold ethics approval from the Human Research Ethics Committee of South Eastern Sydney Local Health District and the University of New South Wales (Sydney), and Addenbrooke's Hospital Local Ethics Committee (Cambridge). In addition, both brain banks comply with the statement of human experimentation issued by the National and Medical Research Council of Australia. Approval for this specific study was obtained

from the University of Sydney Human Research Ethics Committee.

Patients 1–5 underwent detailed clinical assessment by an experienced behavioral neurologist (J.R.H. and/or T.H.B.), as well as formal neuropsychological testing. Patients 1 and 2 were assessed at Frontier, an FTD-specific research clinic based at Neuroscience Research Australia in Sydney. Patients 3–5 were assessed in life at the Disorders of Cognition and Movement Disorders in Cambridge. Patients 6–11 were assessed in life by general neurologists and/or movement disorder specialists. All available records were searched for pertinent information regarding clinical diagnoses and results of neuroimaging.

2.2. Neuropathologic classification into FTLT-tau GGT subtypes

All FTLT-tau cases were reviewed to identify those meeting criteria for GGT. Historically, GGT was often incorrectly classified pathologically as corticobasal degeneration (CBD) or progressive supranuclear palsy (PSP) [19,20,22–24]; therefore, cases previously classified as CBD, PSP, or as unclassified tauopathy were reassessed after publication of the GGT criteria [21]. All cases meeting GGT classification criteria were selected for this study and sub-classified as types I–III. The superior frontal, precentral, and inferior temporal cortices were examined until clear subtype separation was achieved. The precentral cortex was not available from two cases (patients 3 and 4). All pathologic reviews were performed independently and blinded to the clinical features, by three authors (G.M.H., J.J.K., and S.L.F.) experienced in the pathologic diagnosis and sub-classification of tauopathies and GGT. Cases were further sub-typed by two authors (J.J.K. and S.L.F.). Subsequently, any discordantly classified cases ($n = 3$) were reviewed by both researchers together until consensus was reached.

2.3. Immunohistochemistry

Formalin-fixed paraffin-embedded 10- μ m sections were cut from the superior frontal, precentral, and inferior temporal cortices. Immunoperoxidase staining using phosphorylated tau (clone AT8; mouse; 1:1000; Cat. No. MN1012; Thermo Scientific Australia, Scoresby, Victoria) was performed using a Discovery DX autostainer (Ventana Medical Systems, Tuscon, AZ). Sections were counter stained with Hematoxylin.

2.4. Images and figure production

All sections were visualized under a Zeiss Axioskop microscope (Munchen-Hallbergmoos, Germany), and RGB images captured using a Zeiss AxioCam HRC camera and AxioVision 4.7 software. For figure production, only minor adjustments to brightness and contrast were made using the levels command in Adobe Photoshop CS6 (San Jose, CA) to

best represent immunostaining when viewed directly under the microscope.

3. Results

3.1. Patient demographics and clinical features

In total, 11 patients (seven males and four females, mean age at diagnosis 67.3 ± 10.6 years) with neuropathologically confirmed GGT were identified from 181 FTLT-tau cases. The remaining FTLT-tau cases comprised 36 with Pick's disease, 43 with corticobasal degeneration, 89 with progressive supranuclear palsy, one case with neurofibrillary tangle predominant dementia, and one case with argyrophilic grain disease. Demographic and clinical information on each patient with GGT is presented in [Table 1](#). Two illustrative cases are presented below (patients 1 and 2), and additional clinical information on patients 3–5 are presented in [Supplementary Material](#).

3.2. Patient 1

A 76-year-old woman presented with a 2-year history of progressive speech disturbance. The speech became hesitant, with slurring and sound distortion. Early in the course of the illness, she developed “yes”/“no” confusion, producing these responses either randomly or inappropriately. Initially, reading and writing abilities were relatively preserved, as was comprehension. Over time, she demonstrated reduced motivation, rigid behavior, emotional blunting, and her self-care deteriorated. The patient had an identical twin who was fit and well. There was no family history of neurodegenerative disease.

When assessed 4 years after the initial diagnosis, the patient had severe dysarthria. Repetition of simple words was intact, but impairment was noted with more complex words such as “hippopotamus”, “caterpillar”, or “chrysan-

themum”. Dysarthria hampered assessment of anomia, but single word comprehension was preserved. Marked dysgraphia, with gross spelling errors, was noted.

In addition to dysarthria, the patient demonstrated severe orobuccal apraxia, but there was no tongue wasting or fasciculation. Mild rigidity of the right upper limb was noted, but there were no other features of parkinsonism and no other motor signs. Limb apraxia was present bilaterally and symmetrically, with impaired miming of object use and gestures.

On neuropsychological screening, the patient scored 41 of 100 on the Addenbrooke's Cognitive Assessment—Revised (ACE-R, Normal $> 88/100$). She lost points in all cognitive domains, but especially on memory (1/26) and verbal fluency (0/14). Formal neuropsychological testing was limited because of language deficits, but impaired single word repetition and object naming was confirmed. A magnetic resonance imaging (MRI) of the brain revealed mild peri-insular atrophy on the left, but frontal, temporal, and parietal lobe volumes were preserved. The patient died 7 years after diagnosis.

3.3. Patient 2

A 56-year-old man presented with a 3-year history of behavioral changes and language impairment. Social withdrawal and disorganization at work were early symptoms, but disinhibition soon developed and became more prominent. His table manners deteriorated, and he often licked plates and bowls at meals, even when dining with friends in restaurants. He began barking at dogs and tweeting at birds in public. His behavior became stereotyped and ritualistic, and he developed a sweet food preference. Over time, his self-care declined, and he had to be persuaded to change his clothes. He defecated on the bedroom floor on several occasions. Cognitively, the patient's vocabulary diminished and his participation in conversations declined markedly.

Table 1
Clinical presentation and globular glial tauopathy (GGT) subtype

Patient	Age at diagnosis (y)	Duration of illness at death (y)*	Gender	Clinical diagnosis	Pathologic subtype	Affected brain regions on MRI	Symmetrical atrophy on MRI
1	76	7	Female	PNFA	III	Frontal, temporal	+
2	56	4	Male	bvFTD	III	Frontal, temporal, parietal	+
3	61	12	Male	bvFTD (right-temporal variant)	I	Frontal, temporal	–
4	71	17	Male	bvFTD	III	Frontal, temporal, parietal	–
5	65	8	Male	bvFTD	I	Frontal, temporal, parietal	–
6	69	5	Male	bvFTD	III	Frontal, temporal, parietal	+
7	72	9	Female	bvFTD	I	Frontal, temporal	+
8	54	9	Female	bvFTD	III	Not available	N/A
9	86	3	Female	AD	III	Not available	N/A
10	77	2	Male	CBS	II	Frontal, temporal, parietal	–
11	71	4	Male	MSA	II	Frontal, temporal, parietal	+

NOTE. Of 11 patients with GGT, seven presented with behavioral variant frontotemporal dementia (bvFTD), one presented with progressive nonfluent aphasia (PNFA), one with an amnesic Alzheimer's-like syndrome, one with corticobasal syndrome, and one with multiple system atrophy.

*For patients 1–5, the duration of illness is calculated as the time from symptom onset to death, whereas for patients 6–11, the duration of illness is calculated as the time from diagnosis to death.

On assessment, the patient was orientated but had poor grasp of current events. Clear word finding difficulty was present in spontaneous speech, but there were no phonological or syntactic errors. Object naming and single word comprehension were very poor, but single word and sentence repetition were intact. Limb examination revealed no motor deficits, parkinsonism, or limb apraxia.

The patient scored 50 of 100 points on the ACE-R (Normal > 88/100), losing most points on the verbal fluency, language, and memory components. Formal testing demonstrated marked executive impairment, impaired object naming, and impaired word and object knowledge. Syntactic comprehension was also impaired, but visuospatial ability appeared to be preserved.

Magnetic resonance imaging of the brain revealed marked frontal and temporal atrophy (See Fig. 1). The anterior poles and mesial aspects of the temporal lobes were affected bilaterally, with no significant asymmetry. The dorsolateral prefrontal, interhemispheric, and orbitofrontal cortices were affected bilaterally, again with no particular asymmetry. The patient declined quickly and died only 1 year after the initial assessment.

3.4. Patients 3–11

The clinical diagnosis of cases 3–11 can be seen in Table 1. Overall, seven patients were diagnosed clinically with bvFTD. Another case presented with an amnesic syndrome, but no significant behavioral disturbances, and was diagnosed clinically with probable Alzheimer's disease. One case had a progressive nonfluent aphasia (PNFA) pattern. Two cases presented with movement disorder syndromes; one with corticobasal syndrome (CBS) and one with multiple system atrophy (MSA). No GGT cases were diagnosed with MND, either in isolation or in combination with dementia. Of the seven bvFTD patients, two had coexisting memory deficits, and two had coexisting language impairment. The two patients who presented with CBS and MSA were not demented. Parkinsonism was detected in two further patients who presented with behavioral and cognitive impairment. Antemortem MRI results were available on nine cases (See Table 1). Frontal and temporal atrophy were present in all cases, with additional parietal atrophy in six of them. Asymmetrical atrophy was reported in four cases (three left-hemisphere predominant).

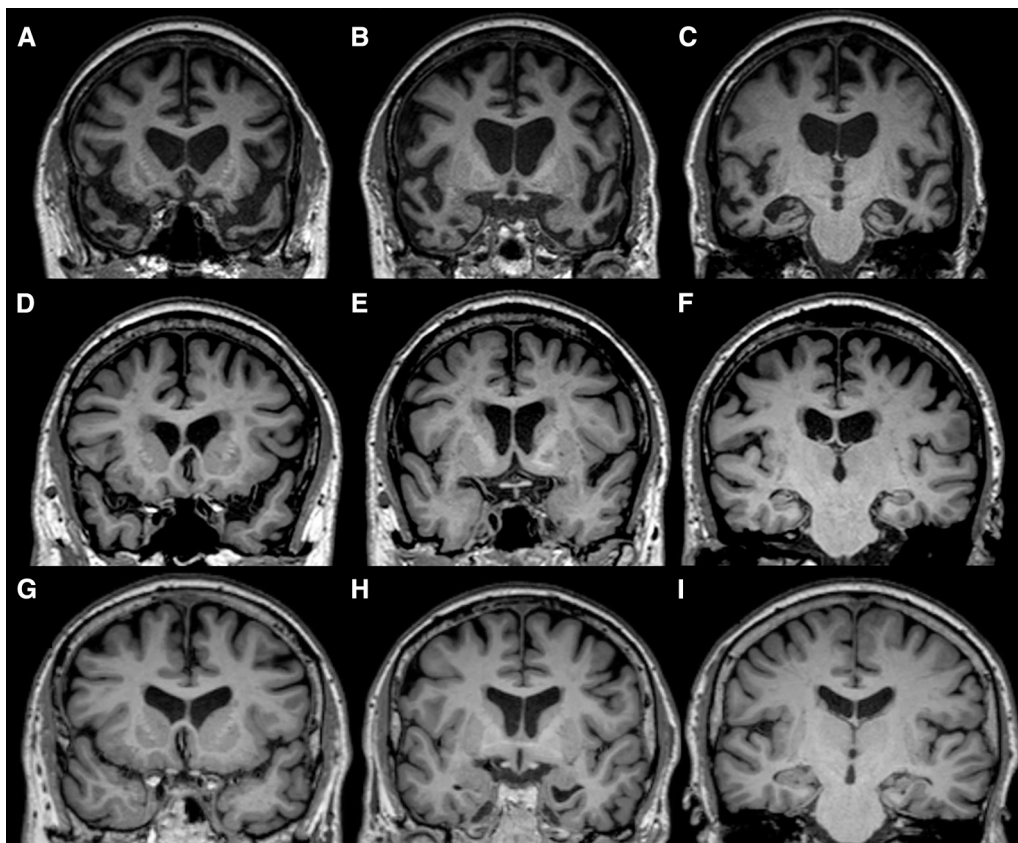


Fig. 1. MRI appearances of globular glial tauopathy (GGT). T1 coronal MRI from patient 2 (first row), a non-GGT FTLT tauopathy (second row), and an age-matched control subject (third row). First row: Sequences taken through the anterior temporal (A), mid-temporal (B), and posterior temporal (C) regions of patient 2. The anterior poles and mesial aspects of the temporal lobes were affected bilaterally, with no significant asymmetry. The dorsolateral prefrontal, interhemispheric, and orbitofrontal cortices were affected bilaterally, again with no particular asymmetry. Second row: A similar pattern of frontal and temporal lobe atrophy is appreciated in a case of pathologically confirmed non-GGT FTLT tauopathy (D–F). Third row: a control subject with normal frontal and temporal volumes (G–I).

3.5. Pathologic classification

All cases had AT8-immunoreactive globular astrocytic and oligodendroglial inclusions in the gray and white matter (Fig. 2A, B, E, F, I, J). All globular astrocytic inclusions were located in proximal astrocytic processes, although their morphology was heterogeneous between GGT subtypes (Fig. 2C, G, K). In contrast, the morphology of globular oligodendroglial inclusions was similar between GGT sub-

types (Fig. 2D, H, L). The distribution of both types of inclusions was heterogeneous between cortices and between the gray and white matter (Fig. 2A, B, E, F, I, J).

Using the classification scheme proposed by Ahmed et al 2013, three cases were classified as type I, two cases as type II and six cases as type III. Type I cases had globular glial inclusions predominantly in the white matter underlying the superior frontal and inferior temporal cortices, with fewer inclusions in the associated gray matter (Fig. 2A, B). In two

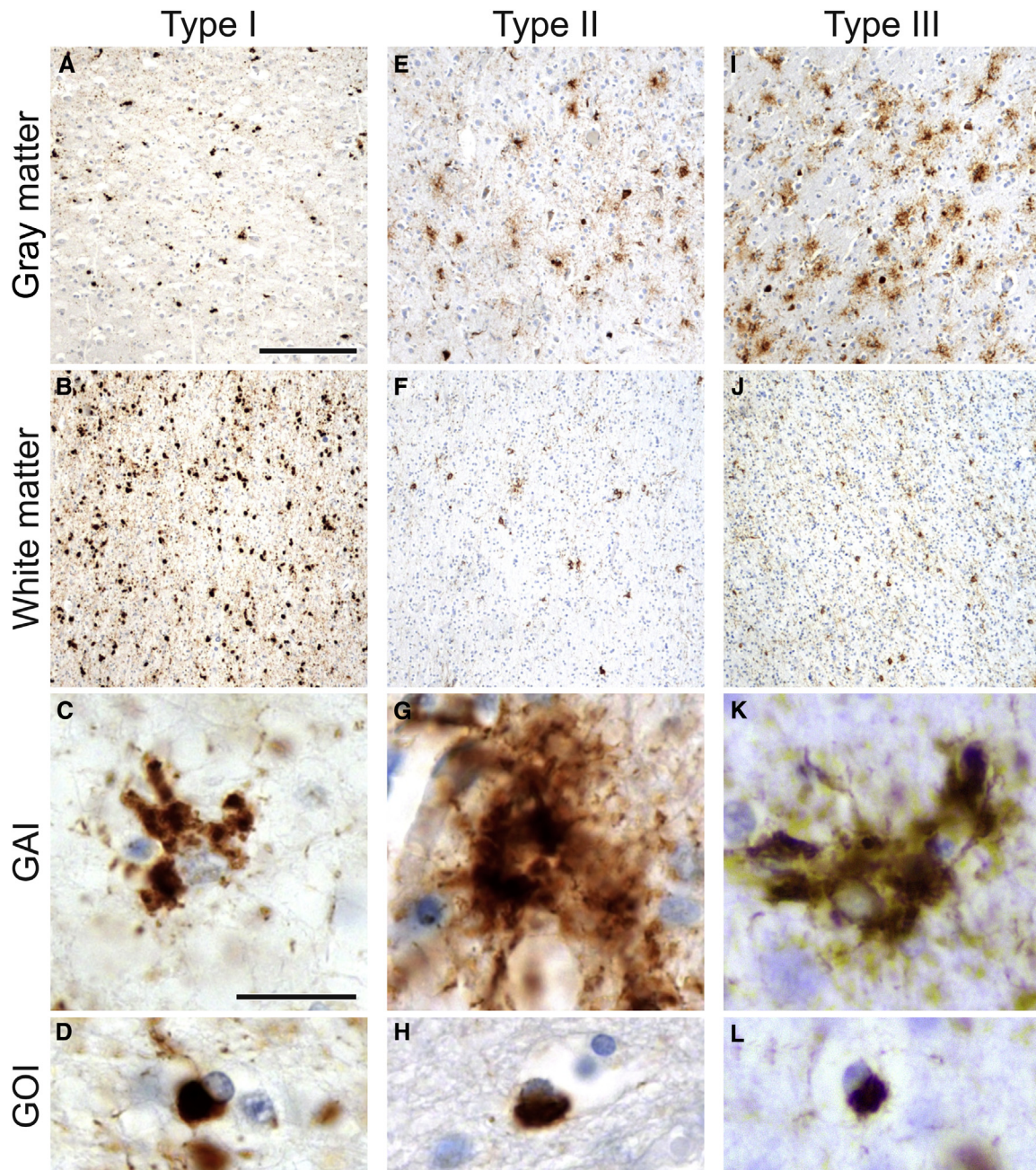


Fig. 2. Distribution and morphology of astrocytic and oligodendroglial pathology in each globular glial tauopathy (GGT) subtype. Representative images in each column are taken from the same case (A–D superior frontal cortex in GGT type I; E–H precentral cortex in GGT type II; I–L superior frontal cortex in GGT type III), and all sections are counterstained with hematoxylin. Scale bar in A = 200 μ m (applies to B, E, F, I, J); 20 μ m in C (applies to D, G, H, K, L). Abbreviations: GAI, globular astrocytic inclusion; GOI, globular oligodendroglial inclusion.

type I cases, globular glial inclusions were sparse in both the gray and white matter of the precentral cortex. A third case was classified as type I, although the precentral cortex was unavailable (patient 3), because of the widespread distribution of globular glial inclusions which predominantly involved the white matter of the superior frontal and inferior temporal cortices. Two of the type I cases were diagnosed clinically with bvFTD, and a third was classified as the right-temporal variant of bvFTD.

In type II cases, the demarcation of gray and white matter AT8-immunopositive pathology was less clear, with a similar prevalence of AT8-immunopositive globular glial inclusions in both regions. In both type II cases, globular glial inclusions predominantly occurred in the precentral cortex (Fig. 2E, F). Both type II cases presented with parkinsonian syndromes (one with MSA and another with CBS), but neither had obvious pyramidal signs or other clinical features of MND.

Type III cases had AT8-immunopositive globular glial inclusions in both gray and white matter in all cortical regions examined (Fig. 2I, J), although the distribution was heterogeneous between cases. The precentral cortex was unavailable in one type III case (patient 4), and emphasis was placed on the prevalence of globular glial inclusions in both the gray and white matter of the superior frontal and inferior temporal cortices. One type III case (patient 1, See [patient demographics and clinical features](#)) was diagnosed clinically with PNFA, but the remainder of type III cases, including patient 2, was diagnosed with bvFTD.

Five GGT cases had less AT8-immunopositive pathology (patients 1, 4, 7, 9, and 10) and were difficult to further subtype and in three of these cases (patients 4, 9, and 10), the researchers were not in agreement. On revision of these cases, consensus was achieved with careful consideration of the distribution between cortices followed by the severity of gray versus white matter pathology.

4. Discussion

The present study demonstrated that although the application of the GGT criteria was achievable, subclassification of cases into types I–III proved problematic, even for experts in the classification of non-Alzheimer's tauopathies. Clinically, GGT patients presented with a variety of different, but overlapping, syndromes. No distinctive clinical syndrome or radiologic characteristic predicted GGT in life. Furthermore, subtyping of GGT into the three subtypes proposed by the consensus criteria did not improve clinicopathologic correlation. The results of this study are important, because they call into question the clinical utility of pathologic subtyping GGT, and indeed, the subtyping of non-Alzheimer's tauopathies more generally. Conversely, the results suggest that more sophisticated clinical phenotyping may not reliably predict underlying GGT or other non-Alzheimer's tauopathies. Finally, given that the analysis of clinical symptoms and signs will never be useful in detecting

asymptomatic or at risk individuals, the results emphasize the need for better biomarkers of tau pathology.

Before discussing the details of the present study in more depth, it is important to consider several potential limitations. First, although the current cohort of GGT represents one of the largest yet assembled, the pathology is rare, and the number of cases available for inclusion was relatively low, despite the availability of a large number of pathologically confirmed non-Alzheimer's tauopathies. The included cases were collected over a long period of time and from multiple sources; this limited the quantity and uniformity of the available clinical data, making detailed clinicopathologic correlation, and statistical analyses, challenging. In particular, it is possible that subtle and clinically insignificant pyramidal signs were underappreciated in the current cohort. Nonetheless, half of the cases, including the two illustrative examples, were seen in specialist clinics and underwent detailed evaluation, providing useful insights. Finally, the precentral cortex was unavailable for two of the cases making subtyping of those particular cases problematic. Ultimately, larger cohorts of GGT patients will be required for relationships between clinical phenotypes and GGT subtypes to be established definitively.

Fundamental application of the diagnostic criteria to identify GGT was straight-forward, but further classification into subtypes I–III was more difficult, especially in cases with less prominent pathology. As demonstrated by BrainNet Europe, consensus is often difficult in neuropathologic diagnosis and further studies taking into account inter-rater reliability are necessary to ensure that GGT subtyping is easily reproducible. However, given that pathologic subtyping of GGT did not appear to improve clinicopathologic correlation in the present study, differentiation of GGT from other non-Alzheimer's tauopathies [18] is likely to be more important for diagnostic purposes.

The previous literature on GGT is based on single case reports [22,23,25–29] or small case series [19,20,24,30–32]; only one previous study of six cases [32] has classified cases according to the proposed subtyping scheme (I–III). A wide variety of clinical phenotypes have been described, but bvFTD [19,20,22,25,26,32] and PNFA [23,27,29,32] presentations are most commonly reported. Some cases have presented with a non-FTD clinical syndrome [24,32]. Indeed, a large proportion of patients in one case series were diagnosed clinically with an atypical PSP phenotype on the basis of rigidity and symmetrical parkinsonism [24]. In terms of motor symptoms and signs, parkinsonism is frequently reported, but it can be symmetrical or asymmetrical [20,24,26,28,30–32]. Pyramidal tract signs appear to be a common, but inconsistent occurrence [19,20,24,28,31,32], with only a couple of studies reporting clinical or neurophysiological evidence of anterior horn cell involvement [31,32]. One very recent report [30] describes severe anterior temporal atrophy in association with the right-temporal variant of bvFTD (right anterior temporal atrophy) and semantic dementia (left anterior temporal

atrophy), but these clinical syndromes have not been described elsewhere.

In the present study, most cases were diagnosed clinically as bvFTD, with one diagnosed as PNFA and two others with atypical parkinsonian syndromes. Unlike other published cases [19,20,24,27,28,31,32] and despite assessments by clinicians (J.R.H. and T.H.B.) with a long-standing interest in MND and FTD-MND, none of our cases had MND or even a predominance of pyramidal signs. None presented with semantic dementia, although one of the bvFTD cases had prominent right-temporal lobe involvement. At a clinical level, the GGT cases were indistinguishable from other bvFTD or atypical parkinsonian syndromes and no distinctive clinical signature of this disease emerged.

Subtyping of GGT pathology does not appear to correlate with any particular clinical phenotype. Only one previous case series subtyped GGT cases according to the consensus criteria [32]. Six cases were reported, but only three presented with clinical features consistent with the proposed pathologic subtype. For example, patient 2 (type I) in that series presented with cognitive symptoms but not FTD. Patient 3 (type III) presented with bvFTD, but no features of MND. Patient 6 (type III) presented with parkinsonism and cognitive symptoms but no behavioral changes or features of MND. Consistent with these findings, GGT subtype correlated poorly with the clinical presentation in the present study. Although the two type II cases were diagnosed with atypical parkinsonian syndromes, neither had features of MND as predicted by the consensus criteria. Of the remaining cases, all of whom presented with bvFTD, PNFA, or an amnesic syndrome, six were sub-classified as type III and three as type I, despite a general absence of MND features and otherwise similar clinical presentations.

If clinical features are unreliable in the detection of GGT and other non-Alzheimer's tauopathies, how can an early and accurate diagnosis of these diseases be made? One of the most promising developments has been the refinement of tau positron emission tomography (PET) ligands. A number of different tau PET ligands have been developed over the last decade, although several challenges remain [33,34]. In particular, many of the early tau ligands were designed to bind to β -pleated sheets [33–35], rather than tau aggregates *per se*, resulting in nonspecific binding to tau and β -amyloid; newer compounds are more specific for tau. Furthermore, isoform predominance (i.e., 3-R or 4-R tau), variability in conformation and post-translational modifications of tau, as well as variability in aggregate ultrastructure may influence binding of potential diagnostic ligands [33–36]. Whether such characteristics vary across the range of non-Alzheimer's tauopathies remains unknown. Encouragingly, ligands may be capable of demonstrating distribution and spread of tau pathology, suggesting potential for diagnosis of specific non-Alzheimer's tauopathies [37].

A new therapeutic era based around manipulation of specific molecular pathologies shows genuine promise for the

treatment of neurodegenerative diseases, but diagnostic and prognostic markers of specific disease entities need to be developed. In the case of GGT, a rare but potentially distinct non-Alzheimer's tauopathy, a clear clinicopathologic correlation has not yet emerged, despite the development of well-considered pathologic criteria. Based on the results of the present study, subtyping of GGT cases as proposed by the consensus criteria is difficult and may not improve clinicopathologic correlation. Longitudinal studies with detailed clinical, neuropsychological, and neuroradiologic characterization, as well as pathologic confirmation, are required to determine if any sensitive and specific markers of GGT, and non-Alzheimer's tauopathies in general, exist.

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Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.dadm.2016.03.006>.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (e.g., PubMed) sources and citations within articles. Key words were globular glial tau (GGT) and frontotemporal dementia.
2. Interpretation: Our findings show that the subtyping of GGT according to the consensus guidelines is difficult and may not improve clinicopathologic correlation.
3. Future directions: Future studies should aim to (1) reassess the value of GGT subtyping with larger cohorts; (2) determine whether biomarkers of tau pathology (e.g., tau PET ligands) are more useful diagnostically.

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