

TITLE PAGE

Title: Neurological rarities: globular glial tauopathy type II

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ABSTRACT

The globular glial tauopathies (GGTs) are a rare group of neurodegenerative diseases with fewer than 90 autopsy-confirmed cases reported in the literature. Although there has been some uncertainty about whether GGT is entirely distinct from progressive supranuclear palsy, a recent study of tau filament structures supports the definition of GGT as a separate neuropathological entity. We present a sporadic case of GGT type II presenting with a progressive corticobasal–primary lateral sclerosis overlap syndrome in a 74-year-old woman. Neuronal and glial tau inclusions were present on neuropathological examination, including globular astrocytic and oligodendroglial inclusions. We also discuss the clinical features and molecular pathophysiology of GGT. Increased awareness of this condition could become more important as patients with GGT may be candidates for anti-tau therapies currently undergoing clinical evaluation in patients with other tauopathies.

INTRODUCTION

Globular glial tauopathies (GGTs) are four-repeat tauopathies characterised by the presence of cytoplasmic globular inclusions found predominantly in oligodendroglia and astroglia¹. They are included in the spectrum of frontotemporal lobar degeneration (FTLD)², and account for less than 10% of all FTLD cases with tau pathology³ (figure 1). They are distinguished from other four-repeat tauopathies based on the globular morphology of phosphorylated tau inclusions, which are distinct from the tufted astrocytes and astrocytic plaques found in progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) respectively¹. In general, GGT presents with varying degrees of frontotemporal dementia (FTD) and upper motor neuron features along with parkinsonism in some cases. We report a case of GGT type II and discuss the clinical and molecular features that distinguish this rare group of conditions from other tauopathies.

CASE HISTORY

A 74-year-old woman presented to a neurologist three weeks after having a fall. She first noticed trouble with her balance two years earlier, when she fell and fractured her L1 vertebra. She was also aware of some weakness in her right arm since then. Her family reported that she had become more irritable and was depressed. They also noticed some cognitive slowing and repetitive speech. Her past history included hypertension, aortic regurgitation and breast cancer treated with surgery and radiotherapy. Her medications were amlodipine, losartan, ranitidine and cholecalciferol. She was retired and did not drink alcohol and had stopped smoking. There was no family history of

neurodegenerative disease; her father died age 80 and her mother age 92. Examination revealed a broad-based and unsteady gait. Her cranial nerve examination was normal. There was slight postural tremor of her hands with bradykinesia on the right side. Her deep tendon reflexes were brisk throughout, with bilateral extensor plantar responses and a positive Hoffman's sign on the right. There was no weakness or sensory loss. Her speech was very tangential with circumlocution, some semantic errors and reduced verbal fluency. She registered five out of eight items by the third trial and retained seven out of eight items after 3 minutes. She performed well on tests of attention, visuospatial and visual perceptual tasks. MRI of her brain revealed moderate small vessel disease. Audio and vestibular testing demonstrated bilateral peripheral vestibular hypofunction with mild to moderate symmetrical sensorineural hearing loss. The vestibular dysfunction was considered long-standing and not the primary cause of her falls.

One year later, she was walking with a frame and falling regularly. Her movement disorder was more prominent with resting tremor and dystonic posturing of the right hand, bradykinesia worse on the right side and increased tone in her right arm. Her DaTscan was abnormal but she did not benefit from levodopa/ benserazide 37.5/150 mg three times daily. Almost five years into the illness, she was unable to walk unaided, had difficulty using her right hand for day-to-day tasks and also noticed that her right leg was clumsy. She developed a staring expression and her vertical saccades were hypometric with a 'round the houses' sign. There was tongue apraxia and she had difficulty copying gestures with her right hand, which tended to wander. Her right leg also tended to lift-up of its own accord. There was no weakness, wasting or fasciculations of the tongue or limb muscles. Her reflexes were pathologically brisk with bilateral finger, pectoralis and crossed adductor jerks along with bilateral Hoffman's sign and upgoing plantar responses. Her central motor conduction times were prolonged bilaterally but there were no lower motor neuron features on neurophysiology. There was evidence of anterior cortical and subcortical dysfunction and bilateral parietal signs on neuropsychometric testing. A repeat MRI scan of her brain showed symmetrical involutinal changes with white matter volume loss mainly in the frontoparietal regions and stable small vessel disease (figure 2). Routine CSF constituents, total and phosphorylated tau, A β and tau/A β ratio were all within the normal ranges. A gene panel, including the microtubule-associated protein tau (*MAPT*) and chromosome 9 open reading frame 72 (*C9orf72*) genes, was negative. The clinical diagnosis was a corticobasal–primary lateral sclerosis overlap syndrome. Her condition continued to deteriorate over the next year and she was no longer able to weight-bear and required continuous care. There was no meaningful use of her right arm and spasticity was managed with baclofen and botulinum toxin injections. She also developed obsessional behaviour and a marked sweet tooth. Her speech became unintelligible and she developed fixed flexion deformities in her

lower limbs during the final year of her life. She died age 79. The disease duration was approximately 7 years.

On macroscopic examination of the brain, there was global volume loss and thinning of the motor cortex. Histological examination (figure 3) revealed severe degeneration of the motor and premotor regions with severe tau pathology affecting both neurons and glia. The neuronal tau inclusions corresponded to neurofibrillary tangles, pretangles and also globular neuronal inclusions. The morphological features of the astrocytic tau inclusions were diverse; many of the astrocytic inclusions were tufted astrocyte-like while others had globular tau deposits compatible with globular astrocytic inclusions (GAIs). A significant proportion of the oligodendroglial inclusions were coiled bodies, but globular oligodendroglial inclusions (GOIs) were also readily found. Low Alzheimer's disease neuropathological change and mild cerebral small vessel disease was also identified. The neuropathological differential diagnosis was between PSP of the primary lateral sclerosis subtype (PSP-PLS) and GGT type II. Although the overall distribution of the tau pathology is similar in both conditions, the tau pathology in GGT type II characteristically includes globular oligodendroglial and astrocytic inclusions with globular deposits. In view of the characteristic microscopic appearances, a diagnosis of GGT type II was made¹.

DISCUSSION

The 2013 consensus recommendations for the diagnosis of GGT defined three pathological subtypes¹. In GGT type I, abundant GOIs are present in the white matter underlying the frontal and temporal cortices¹. GGT type II is also characterised by more abundant GOIs but the pathology is more restricted to the corticospinal tracts¹. In contrast, frequent GAIs in the frontal, temporal and precentral cortices, and anterior horn motor neurons are found in GGT type III¹. Involvement of the corticospinal tracts and anterior horn neurons has also been reported with PSP pathology, and other astrocytic morphologic features, including tufted astrocytes, may be present in cases of GGT, particularly those with GGT type II⁴. These observations have led to some uncertainty about whether such cases should be classified as GGT or atypical PSP with features of GGT^{5,6}. Common to all tauopathies is the ordered assembly of misfolded tau protein into filaments, however these filaments occur in different 3D conformational forms. Using cryo-electron microscopy (cryo-EM), the structure of tau filaments from GGT type I and GGT type II cases have recently been described as showing a common three-layered protofilament fold⁷. Although the GGT fold comprises the same residues as the PSP fold and has a similar three-layered arrangement, each turn has a different conformation compared to its PSP counterpart and the C-terminal domain points in the opposite direction⁷. These findings confirm that tau filaments from GGT type I and GGT type II cases are

distinct from those of PSP, which supports the definition of GGT as a separate disease entity⁷. The seeding properties of GGT-tau may also differentiate GGT from other tauopathies; human GGT brain lysate was shown to have greater tau seeding potency than that from Alzheimer's disease, PSP or CBD⁸. Finally, coexisting proteinopathies seem to be relatively infrequent in GGT and have been reported in less than 10% of previously published cases⁵. Analogous to the α -synuclein immunopositive glial cytoplasmic inclusion pathology found in multiple system atrophy, GGT pathology also preferentially affects glial cells. These observations support an important role for astrocytes and oligodendrocytes in the pathogenesis of neurodegenerative diseases.

A review of 88 GGT cases found that the most common predominant clinical phenotypes are primary progressive aphasia (25.0%) and behavioural-variant FTD (22.7%) followed by upper motor neuron syndromes (12.5%), memory impairment (8.0%), Richardson's syndrome (8.0%), parkinsonism (6.8%), and corticobasal syndrome (6.8%)⁵. However, the clinical syndrome was not very predictive of the neuropathological subtype⁵. GGT may be the most heritable of all FTLD-tau diseases⁹ and of those cases with known *MAPT* gene status, 32.2% had a pathogenic mutation in *MAPT*⁵. The mean age at symptom onset was 54 years for the *MAPT* mutant cases and 70 years for idiopathic cases⁵. The age of onset was similar across all GGT subtypes and the mean disease duration was 7 years for sporadic cases and 6 years for *MAPT* mutant cases⁵. Neuroimaging shows atrophy that is predominantly frontotemporal with additional parietal and/ or precentral involvement in some cases corresponding to the clinical phenotype but not the pathological GGT subtype⁵. Although very rare, patients with this condition may in future benefit from anti-tau therapies currently under investigation for other tauopathies¹⁰. Clinical clues to the diagnosis of GGT type II include prominent upper motor neuron signs, which may be asymmetrical¹¹, in patients with frontotemporal dementia or parkinsonism who may otherwise receive a diagnosis of CBS¹¹, PSP⁴ or a PLS-overlap syndrome as in this case.

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KEY POINTS

1. GGT is a rare neurodegenerative disease characterised by globular phosphorylated tau inclusions in astrocytes and oligodendrocytes.
2. Based on the inclusion morphology and tau filament structure, GGT is considered distinct from other four-repeat tauopathies such as PSP and CBD.

3. Affected individuals typically presents with varying degrees of frontotemporal dementia and upper motor neuron signs with or without parkinsonism.
4. With ongoing research in anti-tau therapies, it may become increasingly important to recognise patients with GGT who may benefit from such treatments in future.

READING LIST

1. Forrest SL, Kril JJ, Kovacs GG. Association Between Globular Glial Tauopathies and Frontotemporal Dementia—Expanding the Spectrum of Gliocentric Disorders: A Review. *JAMA Neurology* 2021;**78**:1004–14.
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Competing interests None declared.

Patient Consent Informed consent was obtained.

Figure 1 Classification of the frontotemporal lobar dementias. FTLD: frontotemporal lobar dementia, TDP43: TAR DNA-binding protein 43, FUS: fused in sarcoma, UPS: ubiquitin-proteasomal system, 3R: 3-repeat tauopathy, 4R: 4-repeat tauopathy, 3+4R: mixed 3- and 4-repeat tauopathy, PSP: progressive supranuclear palsy, CBD: corticobasal degeneration, GGT: globular glial tauopathy, AGD: argyrophilic grain disease, NFTD: neurofibrillary tangle dementia, NIFID: neuronal intermediate filament inclusion disease, a-FTLD-U: atypical FTLD with ubiquitin inclusions, BIBD: basophilic inclusion body disease.

Figure 2 MRI brain performed about 5 years after symptom onset. Sagittal T1 (A, B) and coronal FLAIR images (C-E) show mainly frontal and parietal atrophy with relative preservation of the medial temporal lobe structures. The midbrain to pons ratio is 0.55 (B) - a ratio <0.52 is suggestive of PSP¹². In addition, there is moderate small vessel disease (C-E).

Figure 3 Microscopic findings in a case with globular glial tauopathy, type II. A: The nerve cell loss, neuropil microvacuolation and astrogliosis was severe in the motor cortex while prefrontal cortex was well preserved (B). Tau immunohistochemistry demonstrated a variety of inclusion types. C: A coiled body in the parietal hemispheric white matter. D: Globular oligodendroglial inclusions in the internal capsule and cerebellar white matter (E). F: A globular astrocytic inclusion in the motor cortex. G: A neuron with globular tau positivity in the caudate nucleus. Panels A and B: haematoxylin and eosin, obj. 10, panels C-G: AT8 immunohistochemistry, obj. 20.