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Case Reports

Globular glial tauopathy presenting clinically as atypical parkinsonism with dementia: A clinicopathological case report

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Globular glial tauopathy (GGT) is a primary 4-repeat (4R) tauopathy characterized by aggregates of hyperphosphorylated tau in oligodendrocytes and astrocytes[1]. GGT is categorized into types I, II, and III based on the distribution of tau lesions, which have correlates with clinical presentations[2,3]. Additionally, clinical presentation is highly variable and may share similarities with other primary tauopathies, such as progressive supranuclear palsy (PSP)[4]. Typical signs and symptoms of patients with GGT include behavioral changes, apathy, depression, reduction in motivation, and semantic dementia. GGT may present with motor symptoms, including parkinsonism with concurrent motor neuron disease in some cases. GGT cannot be diagnosed with certainty in life and is most commonly misdiagnosed as behavioral variant frontotemporal dementia (bvFTD)[5,6].

Here we report clinical and neuropathological findings of an individual with GGT type III, who was clinically misdiagnosed first with dementia with Lewy Bodies (DLB) and subsequently with multiple system atrophy (MSA). Descriptions of GGT have predominantly been reported in the dementia literature and many movement disorders specialists have limited awareness of this entity. This clinical presentation of GGT may provide clues to its diagnosis when assessing an atypical parkinsonian syndrome.

1. Case history

The patient was a 65-year-old man who presented to our clinic for consultation with a five-year history of progressive worsening of gait and balance. The patient had no family history of parkinsonism or dementia, but his half-sister and father had tremor. His past medical history was significant for type 2 diabetes mellitus and degenerative spine and disc disease for which he had undergone surgery 6 times. He also reported a longstanding mild hand tremor with action since his 20's. The patient had depression with onset in childhood that was managed with amitriptyline as well as many years of severe anxiety impacting his socialization. Beginning at age 60, he started to develop gait problems. At the same time, his longstanding hand tremor and his bilateral hand dexterity began to worsen. At age 61, his chronic constipation worsened, and he was diagnosed with gastroparesis. By age 62, his gait had worsened to the point where he required a cane for mobility. At age 63, he became wheelchair bound due to frequent falls. Beginning at age 64, in the six to twelve months prior to presentation in our clinic, he developed increasing apathy and continued to have substantial residual depression despite amitriptyline therapy. Within the same time frame, he developed deficits in short-term memory, word finding, and abstract thinking, as well as intermittent stuttering speech. He also developed a tendency to perseverate and to at times engage in compulsive behaviors. In the months prior to presentation, he received a short trial of carbidopa/levodopa (25/100 mg BID) without clear improvement. An MRI performed at age 64, 1 year prior to consultation, demonstrated only mild periventricular white matter changes and mild generalized atrophy (Fig. 1A). Limited electromyography of the lower extremities demonstrated acute and chronic denervation in a left L5 distribution and axonal greater than demyelinating severe sensorimotor peripheral neuropathy.

When the patient first presented to the clinic, his constipation was managed with dietary measures only, symptoms of gastroparesis were mild, and he had urinary urgency and difficulty initiating micturition, but no urinary incontinence. He denied orthostasis or syncope. He denied any symptoms of rapid eye movement sleep behavior disorder though he did report insomnia. He reported his longstanding hand tremor had more recently worsened and was present both at rest and with action.

On initial examination, no orthostatic hypotension was present. His Montreal Cognitive Assessment (MoCA) score performed at age 65 was 13/30 with deficits in every category. Eye movements and cranial nerve examination were normal. He had mild hypophonia and marked hypomimia and no stuttering of speech was present on examination despite his report of these symptoms. There was marked distal (grade 1-2/5) and mild proximal (grade 4-5/5) left leg weakness and atrophy, as well as

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Figure 1

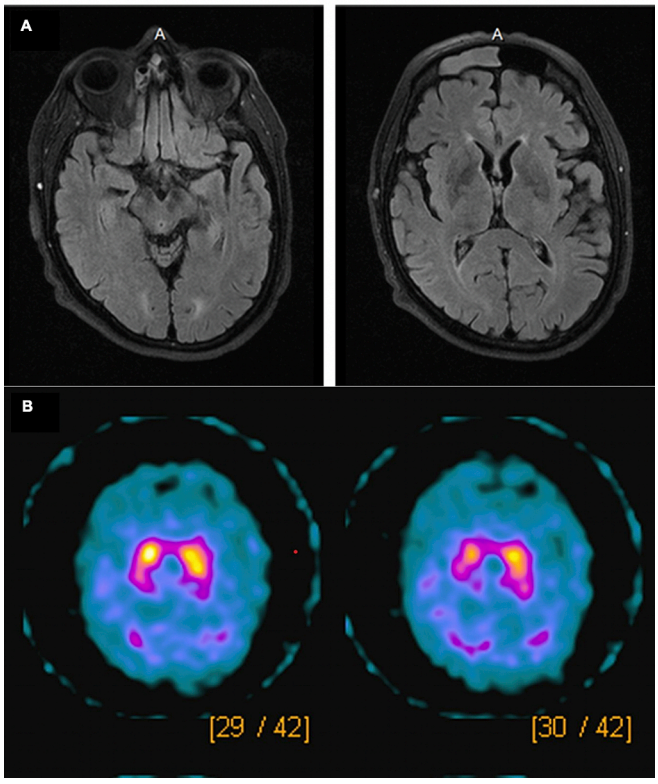

Fig. 1. (A) Axial FLAIR imaging one year prior to presentation. Mild white matter changes and mild generalized atrophy. The MRI does not show midbrain atrophy or striatal abnormalities. (B) DaTscan with heterogenous striatal binding and partial loss of normal comma-shaped morphology bilaterally consistent with a presynaptic dopaminergic deficit.

contracture of the left knee. No other weakness was present. Deep tendon reflexes were trace throughout, and plantar reflexes were non-responsive. He had diminished light touch in the left leg up to his knee and decreased sensation for vibration and pinprick in both feet. The patient had high frequency, low amplitude resting tremor of his jaw and bilateral upper extremities and jerky left greater than right hand postural and action tremor. There was moderate right greater than left sided bradykinesia and rigidity, but no spasticity. He required assistance to stand and was only able to walk a few steps with two person assist.

Neuropsychological testing was performed but was limited because of excessive fatigue. This demonstrated global impairment affecting short term and working memory, visuospatial function, verbal fluency, executive function, and psychomotor speed. The patient had a dopamine transporter single-photon emission computed tomography scan (DaTscan) performed which confirmed dopaminergic deficit. Carbidopa/levodopa was increased up to 1200 mg a day with no response and was subsequently stopped. At this point in the clinical course, the tentative diagnostic impression was DLB superimposed on a polyradiculoneuropathy given the patient's parkinsonism, dementia, lower extremity weakness, and abnormal DaTscan.

The patient was seen 3 more times over the next 12 months. During this period, his depression continued to worsen, and he was taken off amitriptyline. He was given a trial of trazadone and subsequently mirtazapine and nortriptyline, none of which were effective. His gait and balance progressively worsened. When standing with support, he had a high-frequency, low-amplitude jerky tremor of both legs. He developed progressive urinary and fecal incontinence with urinary retention. He was referred to urology where an indwelling catheter was placed, and he was diagnosed with a neurogenic bladder. Though the patient's initial diagnosis was DLB, he did not have hallucinations or motor fluctuations, making this diagnosis less likely. The development of more profound autonomic dysfunction, lack of levodopa response, and progressive weakness led to the clinical diagnosis being revised to MSA-parkinsonian type. He died 13 months after his first consultation.

2. Neuropathological examination

The fixed left hemibrain weighed 590 g, and the calculated whole brain weight was 1180 g. Macroscopic findings revealed moderate cortical atrophy over the dorsolateral frontal lobe, but no temporal lobe atrophy (Fig. 2A). The sagittal plane showed no atrophy in the brainstem or cerebellum (Fig. 2B). The lateral ventricle was moderately enlarged (Fig. 2C). There was mild atrophy of the anterior portion of the amygdala and hippocampal formation. The sections of brainstem and cerebellum were unremarkable (Fig. 2D).

3. Histopathologic finding

On hematoxylin and eosin stained slides, neuronal loss and gliosis were widespread in the motor cortex, premotor cortex, substantia nigra, hippocampus, and the basolateral regions of amygdala. Immunohistochemistry with anti-phospho-tau antibody (CP13) revealed numerous pretangles, globular oligodendroglial inclusions (GOIs) in the white matter and globular astrocytic inclusions (GAIs) in the gray matter in affected cortices (Fig. 2E). The glial inclusions were strongly positive for 4R tau. GOIs were positive on Gallyas silver stain, while GAIs were weakly stained. The distribution of the tau lesions (Table 1) showed that motor cortex and temporal gyrus were both affected, and that GAIs were particularly numerous in the motor cortex. The distribution pattern of tau lesions was consistent with GGT Type III [3]. Of note, there were no tufted astrocytes or astrocytic plaques, excluding the diagnosis of PSP or corticobasal degeneration (CBD).

Thioflavin S fluorescent microscopy revealed no senile plaques or amyloid angiopathy in the neocortex and limbic structures, but sparse neurofibrillary tangles were detected in the hippocampus, motor cortex, superior temporal cortex, and inferior parietal cortex. Immunohistochemistry for α–synuclein did not show any Lewy-related pathology or glial cytoplasmic inclusions, which ruled out Lewy body disease and MSA. Immunohistochemistry for phospho-TDP-43 did not show any pathological aggregates in the basal forebrain and amygdala.

4. Genetic analysis

Genetic testing was performed using a frozen tissue from the right hemibrain. The results for specific alleles are as follows: MAPT H1H1, APOE e3/e3, TMEM106B rs3173615 TT, GRN rs5848 CC, which are all the most common variants.

5. Discussion

This case expands our knowledge of the clinical presentation of GGT by demonstrating a phenotype of complex atypical parkinsonism with rapidly progressive dementia and no evidence of temporal lobe atrophy or semantic dementia. GGT shares many similarities with the clinical presentation of DLB, PSP, CBD, and FTD[7]. It has only been reportedly misdiagnosed as MSA in one other similar case; however, in retrospect it is clear in this case that there were several clinical features that would be very unusual in MSA [8,9]. GGT is classified into three subtypes: Type I, Type II, and Type III. Type I cases typically present with features of bvFTD with apathy, depression, and semantic dementia associated with predominantly fronto-temporal distribution of pathology. Type II cases are characterized by pyramidal features associated with motor cortex and corticospinal tract degeneration. Type III cases can present with a combination of frontotemporal dementia and motor neuron disease[5]. Microscopic pathology seen in GGT typically involves 4R immunoreactive globular oligodendroglial and astrocytic inclusions. The latter are

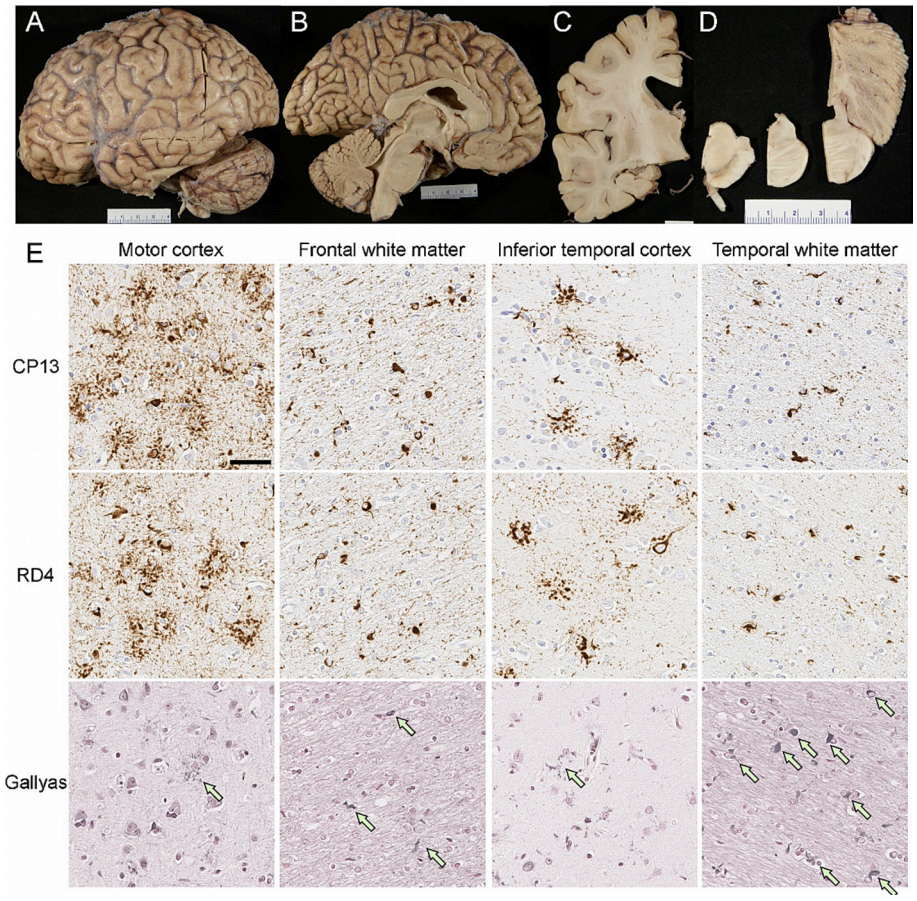

Fig. 2. Representative images of macroscopic and microscopic findings. (A-D) Macroscopic findings show moderate cortical atrophy over the dorsolateral frontal lobe. (B) No atrophy is observed in the brainstem and cerebellum. (C) The lateral ventricle is moderately enlarged. The posterior part of the putamen is preserved. (D) The size of midbrain, pons, and the superior cerebellar peduncle are preserved. (E) Immunohistochemistry with anti-phospho-tau antibody (CP13, from the late Peter Davies), anti-4-repeat tau antibody (RD4, Millipore, Temecula, CA), as well as Gallyas silver staining. CP13 and RD4 immunohistochemistry reveals numerous globular astrocytic inclusions in the motor cortex and inferior temporal cortex, which are slightly stained with Gallyas silver staining (arrows). In the white matter of the frontal and temporal lobes, many globular oligodendrocytic inclusions are observed. These are also positive with Gallyas silver staining (arrows).

mostly negative for Gallyas silver staining. Our case had neuropathological findings most consistent with GGT Type III.

Much of this patient's clinical presentation can be explained by his pathology. The patient presented with levodopa nonresponsive parkinsonism, and he had an abnormal DaTscan (Fig. 1B). His pathology demonstrated neuronal loss in the substantia nigra as well as diffuse basal ganglia tau pathology, which correlates with his lack of levodopa response. The patient initially had mild weakness and sensory impairment in the lower extremities. The rapid progression of his lower extremity weakness is not fully explained by his diabetic peripheral neuropathy and/or radiculopathy due to degenerative spine disease and may have been due to motor neuron disease associated with neuronal loss, tau inclusions, and GAIs in his motor cortex. Primary motor cortex involvement has been noted in other reports of GGT[7]. His depression and anxiety began long before any other cognitive, motor, or behavioral symptoms; however, his increasing apathy and depression may be correlated with his orbitofrontal tau pathology. Development of perseveration and compulsive behaviors is consistent with the FTD-like presentation noted in many cases of GGT type III[5]. One recent case series shares similar observations suggesting that an FTD-like syndrome that evolves into a Parkinson-plus syndrome with speech apraxia with preserved midbrain volume, as well as possible lower motor neuron involvement, may be suggestive of underlying GGT pathology[7]. Unique features in this patient include rapidly progressive multi-domain dementia with no preferential language dysfunction or semantic dementia, which differs from most patients with pathologically confirmed GGT types I and III [47]. Similarly, the cause of his autonomic failure remains unclear; however, his longstanding history of diabetic autonomic neuropathy and subsequent severe dementia likely contributed to his urinary and fecal incontinence and makes it impossible to ascribe these problems to GGT pathology alone.

Throughout the course of this patient's treatment, he had some clinical features resembling both DLB and MSA. Though in retrospect, he never met full diagnostic criteria for either and there was no evidence of pathology consistent with MSA or Lewy body disease with α-synuclein immunohistochemistry[10]. The patient's initial diagnosis of DLB superimposed on polyradiculoneuropathy did not fit as he did not exhibit day-to-day fluctuations or visual hallucinations as seen in DLB. The development of apparent autonomic dysfunction (e.g., urinary retention) along with upper extremity jerky postural and action tremor, and lower motor neuron signs led his diagnosis to be changed to MSA[11–14]. His progressive weakness was also thought to be due to MSA though this is a non-specific finding of MSA. The patient had no evidence of myoclonus, head drop, stridor, orthostatic hypotension as might be seen in MSA; and his low MoCA score with severe cognitive impairment and rapidly progressive dementia is not typical for MSA. Additionally, his deficit in visuospatial function on neuropsychological testing is an atypical feature of MSA[15]. His abnormal DaTscan findings are not specific to DLB or MSA, however to our knowledge, there is no other report of DaTscan findings in a patient with pathologically proven GGT. His autonomic dysfunction included gastroparesis with later development of bowel and bladder dysfunction and might have been largely due to his diabetes and global dementia. The patient had hypophonia and described stuttering (although this was not present on examination), both of which may be present in many synucleinopathies and tauopathies[7]. At this point in the course of treatment, an FDG-PET study may have been useful to assess for reduced metabolism in the occipital lobes as may be seen in patients with DLB or reduced metabolism in the basal ganglia and cerebellum as may be seen in MSA[16,17]. Similarly, frontal, caudate, midbrain and thalamic hypometabolism has been noted in 4R-tauopathies such as GGT[18]. Other causes of atypical parkinsonian syndromes such as atypical PSP with corticospinal tract involvement, CBD, and FTD with motor

Table 1
Anatomic distribution of tau lesions assessed with phospho-tau immunohistochemistry.

Region	Tau (+) neuronal inclusions	Tau (+) oligodendroglial inclusions	Tau (+) astrocytes	Tau (+) threads
Temporal cortex	++	+++	+++	+
Superior frontal gyrus	+++	+++	+++	+
Motor cortex	+++	+++	+++	+++
Caudate/ putamen	+++	+++	+++	+
Globus pallidus	++	++	–	++
Basal nucleus	+++	+++	++	++
Hypothalamus	+++	++	+	+++
Ventral thalamus	+	+++	+	+++
Subthalamic nucleus	++	++	++	++
Thalamic fasciculus	–	+++	–	+++
Red nucleus	++	+++	–	++
Substantia nigra	++	+++	++	+++
Oculomotor complex	+++	+	–	+
Midbrain tectum	++	+++	++	+++
Locus coeruleus	++	–	–	+
Pontine tegmentum	++	+++	+	++
Pontine base	+	+	–	+
Medullary tegmentum	++	++	+	++
Inferior olivary nucleus	+	+	–	+
Dentate nucleus	++	–	–	+
Cerebellar white matter	–	+	–	–

neuron disease were considered in the differential diagnosis during the care of this patient. Though dementia in GGT is common, this case differs from many previously reported because the patient did not exhibit preferential language dysfunction or semantic dementia. The complexity of this case highlights the difficulty in assigning clear diagnostic criteria to GGT and the necessity for GGT to be among the differential diagnosis for patients with atypical parkinsonism.

In summary, as clinico-pathologic correlation is carried out on more GGT cases, a novel phenotype of GGT which presents as an atypical parkinsonian syndrome may begin to be differentiated in life from more common tauopathies and synucleinopathies. GGT is relatively well known amongst dementia specialists but there have been few cases reported in the movement disorders literature. With expanded awareness of GGT among the movement disorders community, we suspect that GGT will be more often considered in the differential diagnosis of atypical parkinsonism. GGT has never been correctly diagnosed in life, but future development of fluid and tissue biomarkers may allow for this by differentiating GGT from synucleinopathies and other tauopathies. At this time, structural imaging with MRI does not provide enough specificity to differentiate GGT from other neurodegenerative disorders such as FTD[7]. In patients with FTD, genetic testing for *C9orf72* mutation may be a very useful tool particularly when the symptoms coincide with neuropsychiatric conditions as carriers of this mutation are at an increased risk of psychiatric disorders[19]. The development of novel tau, synuclein, and other PET imaging techniques as well as more specific genetic testing might also allow for the specific diagnosis of GGT and the exclusion of other neurodegenerative pathologies.[18,20]

6. Ethical Compliance Statement

The authors confirm that the approval of an institutional review board was not required for this work. Consent from next of kin for autopsy and analysis of the pathology was obtained. All patient data has been anonymized and patient informed consent was not required as this is a retrospective case report and next of kin consent was obtained. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The brain donation was made with coordination provided by the Brain Support Network. No support from NIH grants are relevant for this case. The writing of this case-report did not require any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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