


## SHORT COMMUNICATION

# Corpus callosum hypersignals and focal atrophy: Neuroimaging findings in globular glial tauopathy type I

Jiri Keller<sup>1,2</sup> | Anna Kavkova<sup>1,2</sup> | Radoslav Matej<sup>2,3</sup> | Zsolt Cséfalvay<sup>4</sup> |  
Robert Rusina<sup>2,5</sup> 

<sup>1</sup>Department of Radiology, Na Homolce Hospital, Prague, Czech Republic

<sup>2</sup>Third Faculty of Medicine, Charles University, Prague, Czech Republic

<sup>3</sup>Department of Pathology and Molecular Medicine, Thomayer University Hospital, Prague, Czech Republic

<sup>4</sup>Department of Communication Disorders, Comenius University, Bratislava, Slovakia

<sup>5</sup>Department of Neurology, Thomayer University Hospital, Prague, Czech Republic

## Correspondence

Robert Rusina, Department of Neurology, Charles University, 3rd Faculty of Medicine, Thomayer University Hospital in Prague, Videnska 800, 140 59 Praha 4, Czech Republic.  
Email: robert.rusina@lf3.cuni.cz

## Funding information

Thomayer University Hospital, Grant/Award Number: TN 006419; Na Homolce Hospital, Grant/Award Number: NNH 00023884; Czech Ministry of Health, Grant/Award Number: NV19-04-00090 and NV18-04-00346; Charles University, Prague, Grant/Award Number: Progress Q35/LF3

## Abstract

**Background and purpose:** Globular glial tauopathies (GGTs) have heterogeneous presentations; little evidence regarding typical clinical and magnetic resonance imaging (MRI) presentations are available.

**Methods:** We retrospectively assessed MRIs from three postmortem-confirmed GGT cases, in two patients with atypical progressive aphasia and one with corticobasal syndrome.

**Results:** We suggest that four principal concomitant MRI findings characterize GGT type I: a sagittal callosal hyperintense band, marked focal callosal atrophy suggesting white matter degeneration originating in cortical areas responsible for symptoms (anterior atrophy in predominantly language manifestations and posterior atrophy in predominantly apraxia), periventricular white matter lesions, and mild-to-moderate brain stem atrophy.

**Conclusions:** We observed four concomitant MRI abnormalities in patients with atypical dementia, parkinsonism, and late incomplete supranuclear gaze palsy. Two patients had atypical progressive aphasia and one had corticobasal syndrome.

## KEYWORDS

corpus callosum, dementia, globular glial tauopathy, magnetic resonance, tauopathy

## INTRODUCTION

Globular glial tauopathies (GGTs) have heterogeneous presentations [1]; little evidence regarding typical clinical and magnetic resonance imaging (MRI) presentations is available. We report MRI findings for three autopsy-confirmed GGT cases, two presenting clinically with atypical primary progressive aphasia (PPA) and one with corticobasal syndrome (CBS).

## METHODS

The first case (previously published) was a 69-year-old man with a combination of two PPA subtypes (i.e., early nonfluent-agrammatical and late semantic variant) and hippocampal amnesia [2]. He initially had mild anomia, without language comprehension impairment at the single word and sentence level. Progressively, he developed lexical retrieval problems, speech apraxia, and

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. *European Journal of Neurology* published by John Wiley & Sons Ltd on behalf of European Academy of Neurology.

agrammatism in spontaneous speech. Early memory impairment was present, mainly as delayed verbal recall and total verbal learning ability.

Dopa-unresponsive right-sided rigidity, hypokinetic dysarthria, and supranuclear oculomotor palsy with slowed voluntary saccades appeared during the 4th year of disease progression. Oral and written language production and comprehension were impaired at the single word and sentence level; few content words remained in his speech.

During the 5th year, he lost comprehension skills and became almost mute, using only nonverbal communication. He also began to express executive and behavioral symptoms, namely, perseveration, emotional blurring, alternating apathy and disinhibition, and episodic compulsive laughter. The patient died later that year.

A 76-year-old man developed progressive aphasia, memory difficulties, and fluctuating emotional control. He had diminished ability for verbal expression and impaired word repetition of multisyllabic words (oral apraxia), and only monosyllabic vocalization was preserved. He also had severely impaired comprehension skills at the sentence level, but single word comprehension remained partially preserved, suggesting the PPA nonfluent/agrammatic variant.

Three years later, verbal expression had become extremely poor, with anomia, agrammatism, and bradypsychia. Comprehension at the sentence level and for complex orders became impaired. Progressively, akinesia with rigidity and supranuclear oculomotor palsy developed, with severe executive dysfunction (stereotypical behaviors, perseveration, apathy, and hyperorality). Six years after disease onset, his speech was almost unintelligible, and he was unable to state his desires and needs verbally; he expressed his feelings using vocal modulation of perseverated single words and syllabic compounds. The patient died the following year.

A 72-year-old man developed, over 3 years, gait instability with unprovoked falls and clumsiness of his left hand. Neurological examination found asymmetric parkinsonism with akinesia and rigidity, spastic left-sided hemiparesis with hyperreflexia, and left-hand apraxia. Neuropsychology showed deficits in conceptualization and planning with impaired working memory and concentration skills; CBS was diagnosed, and levodopa was introduced, but with little improvement.

Two years later, intermittent involuntary dystonic movements of his left upper extremity with focal myoclonus appeared, consistent with the alien hand phenomenon typical of CBS. Walking was almost impossible due to a combination of gait apraxia, rigidity, and spastic contractures with dystonia in the left lower extremity. The patient had mild hypokinetic dysarthria and pharyngeal dysphagia, with no impairment of language processes in production or comprehension. During the following year, he became wheelchair bound, and supranuclear oculomotor palsy was a late finding in the disease course before his death.

In the post hoc MRI analysis, high-resolution (1-mm isotropic voxel) three-dimensional T1-weighted images acquired on single 1.5T MRI (Siemens Avanto), available in all subjects, were

reconstructed in the sagittal plane, and ImageJ software was used to manually segment the corpus callosum (CC) according to two widely used segmentation schemes, Witelson's plus Hofer and Frahm's [3,4].

## RESULTS

MRIs showed similar findings in Cases 1 and 2, mainly marked by fluid-attenuated inversion recovery (FLAIR) hyperintensities and anterior atrophy of the CC, periventricular white matter lesions (WMLs), and mild brain stem atrophy (Figure 1a–f). In Case 1, cortical atrophy predominated in the temporal lobes and hippocampi (more on the left). Subcortical atrophy led to the widening of the ventricles. As an additional finding, an unrelated large hyperintense postischemic lesion was found in the right parietal lobe on T2-weighted images.

Case 2 showed atrophy of the left temporal and dorsotemporal cortex with pronounced atrophy of both hippocampi. Subcortical atrophy with mild ventricular dilatation and periventricular FLAIR hyperintensities were also present.

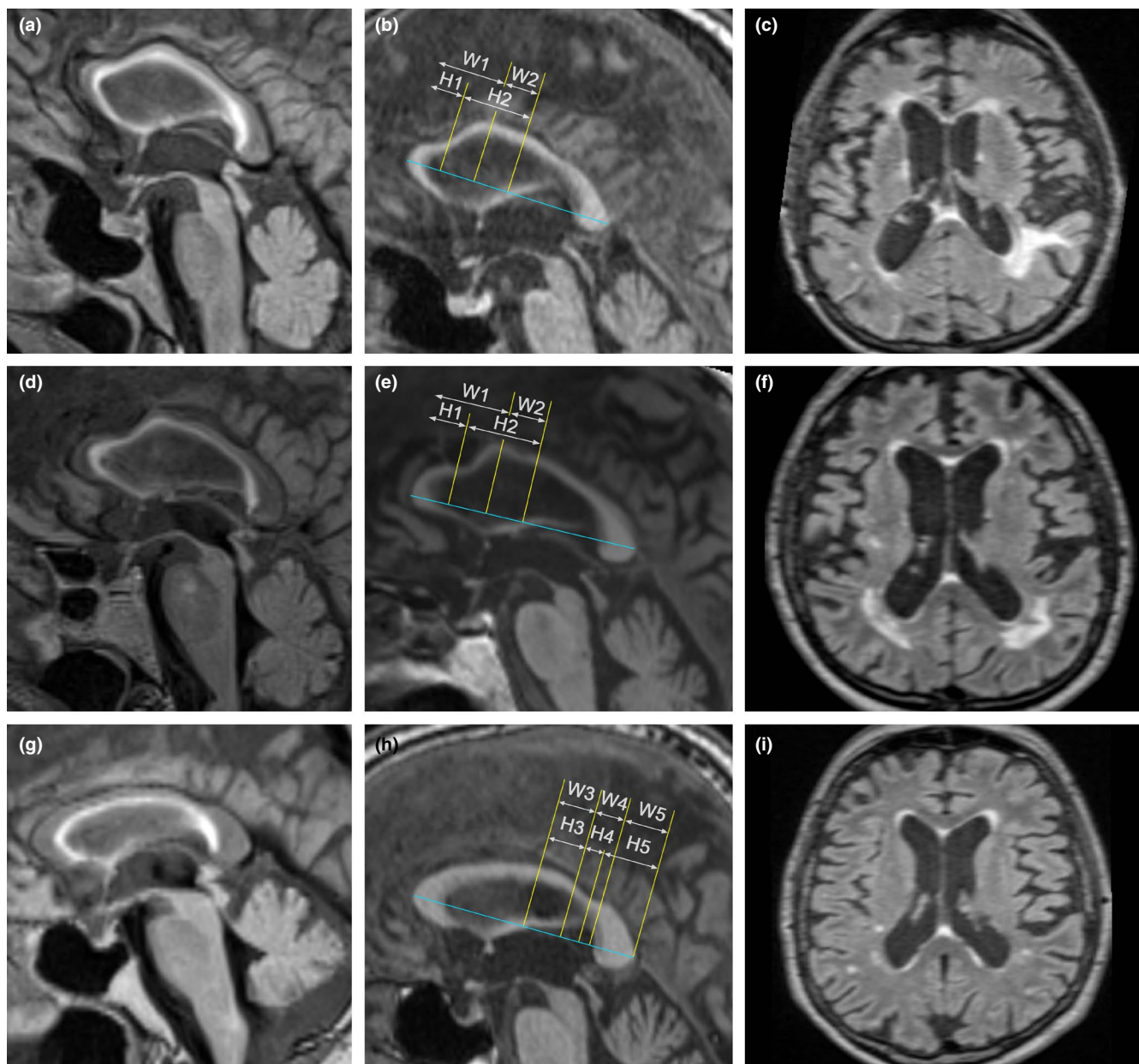
In Case 3, MRI found FLAIR callosal hypersignals and focal atrophy in the posterior part of the CC, together with periventricular WMLs and moderate midbrain atrophy (Figure 1g–i). Cortical atrophy predominated in both parietal and temporal lobes, being most pronounced in the right parietal lobe.

We focused in particular on CC volumetry. In Cases 1 and 2, with PPA, anterior callosal atrophy predominated in Witelson Segment 1 (W1) and Hofer and Frahm Segments 1 and 2 (H1, H2) (Figure 1b,e). W1 contains fibers from the prefrontal, premotor, and supplementary motor areas; H1 fibers project to the prefrontal cortex; H2 fibers project from the premotor and supplementary motor cortex.

In Case 3, with CBS, posterior callosal atrophy was localized in W4, H4, and H5 (Figure 1h). W4 fibers project to posterior parietal and superior temporal cortices, H4 fibers project to the primary sensory cortex, and H5 fibers project from the parietal, temporal, and occipital cortices.

Neuropathology, which was available in all cases, showed diffuse vascular changes to different degrees, neuronal loss, gliosis, and spongy vacuolation of the superficial layers of the frontal and temporal cortices. Hyperphosphorylated tau protein-positive neuronal deposits and oligodendroglial globular inclusions, white matter granular deposits, and globular nonargyrophilic astroglial inclusions fulfilled the diagnostic criteria of GGT predominantly type I [1]. In Case 3, the marked left hemiplegia present from the early stages of the disease correlated with the degeneration of the pyramidal tracts and tau inclusions in the cerebral peduncles, medullary pyramids, and lateral funiculus.

In addition to GGT, other copathologies were found, including limbic-predominant age-related TDP-43 encephalopathy in Case 1 and tauopathies of various types, primarily age-related neurodegenerations such as primary age-related tauopathy, aging-related tau astroglial pathology in Case 2, and tau protein deposits that



**FIGURE 1** Magnetic resonance imaging findings. (a–c) Data from Case 1. (d–f) Data from Case 2. (g–i) Data from Case 3. The left column presents sagittal three-dimensional fluid-attenuated inversion recovery (FLAIR) showing a band of hyperintensity along the bottom edge of the corpus callosum (a, Patient 1; d, Patient 2; g, Patient 3), and mild-to-moderate midbrain atrophy. The middle column represents a midsagittal T1-weighted image showing the atrophy of the corpus callosum (b, anterior atrophy in Patient 1; e, anterior atrophy in Case 2; h, posterior atrophy in Case 3). The right column demonstrates nonspecific periventricular white matter changes to variable degrees on transverse FLAIR slices (c, Case 1; f, Case 2; i, Case 3). H, Hofer and Frahm segment; W, Witelson segment [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

correlated with the diagnosis of early progressive supranuclear palsy (PSP; Williams PSP tau score = 2–3, Kovacs stage = 3) in Case 3 [5,6].

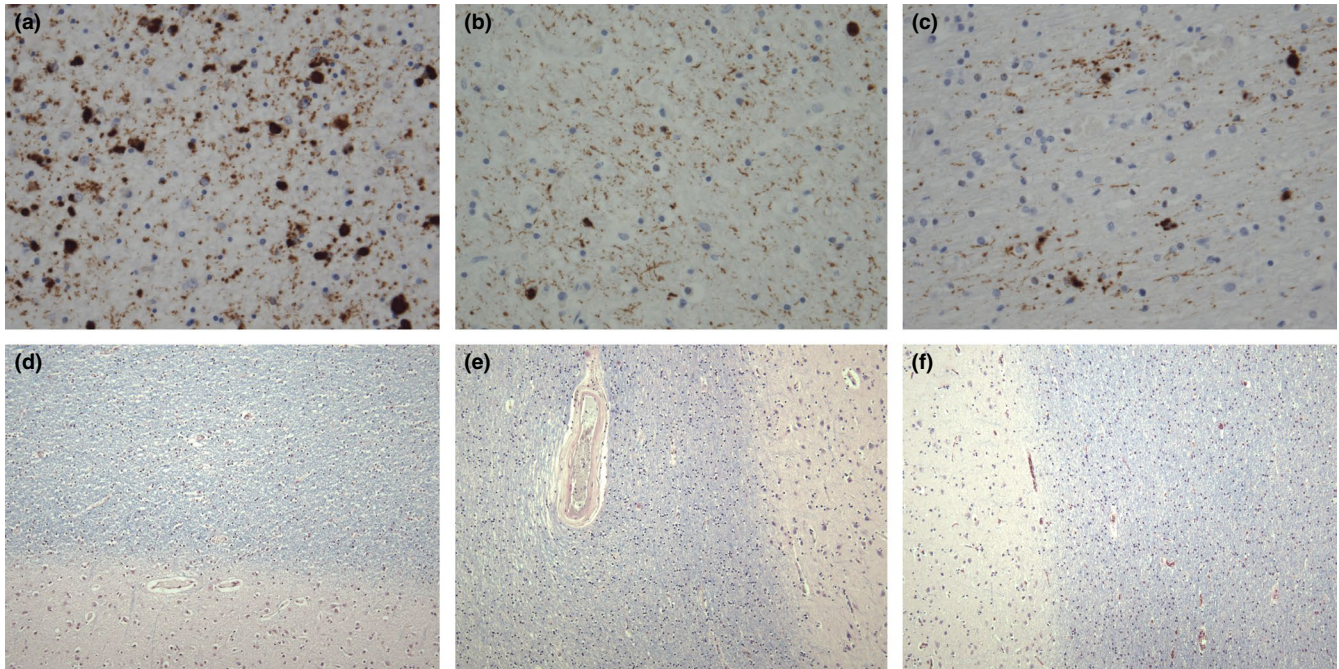
## DISCUSSION

GGT are four-repeat tauopathies that have a variable clinical presentation, with mainly oligodendroglial and astrocytic inclusions; the

most frequent GGT, type I, has severe white matter involvement [1]. GGT is a recently discovered rare disease, and MRI findings are limited; nonspecific WMLs, frontotemporal atrophy, and cerebral peduncle atrophy have been reported [7–11].

We retrospectively assessed MRIs from three postmortem-confirmed GGT cases (Figure 1) and were surprised by an unusual but clearly visible band of uniform hyperintensity on the underside of the atrophic CC. In previously published cases, brain stem atrophy and subcortical WMLs were present but much less prominent [7].





**FIGURE 2** Neuropathological findings. (a–c) Immunostaining for phospho-tau (AT8) reveals characteristic globular oligodendroglial inclusions in the white matter to different degrees in all three patients (a, Case 1; b, Case 2; c, Case 3). Original magnification,  $\times 400$ . (d–f) Comparison of the different degrees of vascular changes in the periventricular white matter in the area of the most prominent nonspecific signal as seen on magnetic resonance imaging scans (d, Case 1; e, Case 2; f, Case 3). Original magnification,  $\times 200$ , Luxol fast blue staining [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

We thus suggest four principal concomitant MRI findings to characterize GGT type I. First is the sagittal callosal hyperintense band, which is uncommon in neurodegenerative or vascular dementia.

Second, marked focal callosal atrophy— anterior (maximum in W1/H2 overlap) in both PPA cases and posterior (maximum W4) in the CBS case— suggests white matter degeneration originating in cortical areas responsible for symptoms (anterior atrophy with predominantly language manifestations and posterior atrophy in prevalent visuospatial dysfunction and apraxia). Specific atrophy has been previously reported in frontotemporal lobar degeneration, Alzheimer disease (AD), and PSP [12] but has primarily been studied in AD [13].

Third, mild-to-moderate midbrain atrophy is in line with incomplete supranuclear gaze impairment; however, diagnostic criteria for PSP were not met. Fourth, periventricular WMLs, although nonspecific, were linked to GGT type I; WMLs and atrophic cerebral peduncles were also reported in GGT types II and III [7,9,11]. Although these imaging abnormalities may be present in other neurodegenerative conditions, their combination may be unique for patients diagnosed with GGT.

Neuropathological correlations are depicted in Figure 2. A particular pattern of GGT is the almost constant involvement of glial elements in the cerebral white matter [14]. Figure 2a–c compares deposits of hyperphosphorylated tau protein visualized using an immunohistochemical reaction with the AT8 antibody clone from the same area of subcortical white matter in all three patients. Moreover, Figure 2d–f demonstrates the different degrees of vascular changes in the posterior third of periventricular white matter

visualized using a histochemical reaction with Luxol fast blue. The samples are taken from the same area where the maximum number of unspecific changes were visible on MRI scans in all three cases.

Neuropathological examination of the CC region did not detect any particular abnormalities despite nonspecific gliosis. These findings support the hypothesis that the observed marked focal callosal atrophy reflects the underlying loss of cortical projections rather than GGT-specific patterns.

## CONCLUSIONS

We observed four concomitant MRI abnormalities in patients with atypical dementia, parkinsonism, and late incomplete supranuclear gaze palsy with a definite neuropathological diagnosis of GGT. Two patients had atypical progressive aphasia, and one had corticobasal syndrome. Further studies are needed to confirm whether these findings are a specific diagnostic hallmark of GGT.

## ACKNOWLEDGMENTS

Written informed consent to publish the results of this study was obtained from the patients' families. The authors thank Thomas Secret for revision of the English version of this article. This study was supported by resources from the Czech Ministry of Health (research programs NV18-04-00346 and NV19-04-00090), by Charles University (Project Progress Q35/LF3), by Thomayer University Hospital (TN 006419), and by Na Homolce Hospital (NNH 00023884). The study protocol was approved by the Multicentric

Ethics Committee of the Institute of Clinical and Experimental Medicine and Thomayer University Hospital in Prague, Czech Republic (approval no. G1827).

### CONFLICT OF INTEREST

None of the authors has competing interests concerning the study or data.

### AUTHOR CONTRIBUTIONS

**Jiri Keller:** Conceptualization (equal), writing–original draft (equal), writing–review & editing (equal). **Anna Kavkova:** Data curation (equal), investigation (equal), validation (equal). **Radoslav Matej:** Conceptualization (equal), funding acquisition (equal), methodology (equal), writing–review & editing (equal). **Zsolt Cséfalvay:** Data curation (equal), investigation (equal), validation (equal). **Robert Rusina:** Conceptualization (equal), funding acquisition (equal), methodology (equal), supervision (lead), writing–original draft (lead), writing–review & editing (lead).

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

### ORCID

Robert Rusina  <https://orcid.org/0000-0002-3864-5459>

### REFERENCES

- Ahmed Z, Bigio EH, Budka H, et al. Globular glial tauopathies (GGT): consensus recommendations. *Acta Neuropathol.* 2013;126:537-544.
- Rusina R, Csefalvay Z, Kovacs GG, et al. Globular glial tauopathy type I presenting as atypical progressive aphasia, with comorbid limbic-predominant age-related TDP-43 encephalopathy. *Front Aging Neurosci.* 2019;11:336.
- Witelson SF. Hand and sex differences in the isthmus and genu of the human corpus callosum. A postmortem morphological study. *Brain.* 1989;112:799-835.
- Hofer S, Frahm J. Topography of the human corpus callosum revisited–comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *NeuroImage.* 2006;32:989-994.
- Williams DR, Holton JL, Strand C, et al. Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson's syndrome. *Brain.* 2007;130:1566-1576.
- Kovacs GG, Lukic MJ, Irwin DJ, et al. Distribution patterns of tau pathology in progressive supranuclear palsy. *Acta Neuropathol.* 2020;140:99-119.
- Ohno Y, Ikeda T, Sakurai K, et al. Rapid progression of white matter signal changes and frontotemporal atrophy in globular glial tauopathy. *J Neuropathol Exp Neurol.* 2021;80:480-483.
- Hirano M, Iritani S, Fujishiro H, et al. Globular glial tauopathy Type I presenting with behavioral variant frontotemporal dementia. *Neuropathology.* 2020;40:515-525.
- Tanaka H, Kawakatsu S, Toyoshima Y, et al. Globular glial tauopathy Type II: Clinicopathological study of two autopsy cases. *Neuropathology.* 2019;39:111-119.
- Josephs KA, Katsuse O, Beccano-Kelly DA, et al. Atypical progressive supranuclear palsy with corticospinal tract degeneration. *J Neuropathol Exp Neurol.* 2006;65:396-405.
- Liu AJ, Chang JE, Naasan G, et al. Progressive supranuclear palsy and primary lateral sclerosis secondary to globular glial tauopathy: a case report and a practical theoretical framework for the clinical prediction of this rare pathological entity. *Neurocase.* 2020;26:91-97.
- Yamauchi H, Fukuyama H, Nagahama Y, et al. Comparison of the pattern of atrophy of the corpus callosum in frontotemporal dementia, progressive supranuclear palsy, and Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* 2000;69:623-629.
- Frederiksen KS. Corpus callosum in aging and dementia. *Dan Med J.* 2013;60:B4721.
- Forrest SL, Kril JJ, Kovacs GG. Association between globular glial tauopathies and frontotemporal dementia–expanding the spectrum of gliocentric disorders: a review. *JAMA Neurol.* 2021;78:1004-1014.

**How to cite this article:** Keller J, Kavkova A, Matej R, Cséfalvay Z, Rusina R. Corpus callosum hypersignals and focal atrophy: Neuroimaging findings in globular glial tauopathy type I. *Eur J Neurol.* 2022;29:324–328. <https://doi.org/10.1111/ene.15090>