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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.

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 ß-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 clinicopathological 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 FTLD-tau GGT subtypes

All FTLD-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-μm 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