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# Corticospinal tract degeneration and temporal lobe atrophy in frontotemporal lobar degeneration TDP-43 type C pathology

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Frontotemporal lobar degeneration (FTLD) consists of a clinically, pathologically and genetically heterogeneous group of neurodegenerative disorders that chiefly affect frontal and temporal lobes. Clinical presentation in FTLD includes behavioural variant frontotemporal dementia, progressive nonfluent aphasia and semantic dementia (SD). Pathologically, FTLD is subdivided based on accumulation of abnormal intracellular proteins including transactivation response DNA-binding protein 43 kDa (TDP-43) [1, 2]. TDP-43 pathology in FTLD is classified into five pathological subgroups depending on its morphological features: TDP-43 type A, B, C, D and E [2, 3]. SD is closely associated with TDP-43 type C, indicating a distinctive pattern of clinical and pathological presentations in TDP-43 type C [2]. It has been demonstrated by Josephs et al. that corticospinal tract degeneration (CTD) can be found in a proportion of patients with TDP-43 type C pathology with a predilection to involve the right temporal lobe [4]. Here, we present an autopsy case of a 65-year-old woman with a 12-year history of a right temporal lobe dominant SD in which TDP-43 type C pathology was found along with CTD. We also provide data on CTD and laterality of temporal lobe atrophy in all the archival cases with a pathological diagnosis of TDP-43 type C in the Queen Square Brain Bank (QSBB) collected between 1991 and 2018.

A right-handed woman with no family history of dementia developed difficulties recognising familiar faces at the age of 53. Her family members also noticed a change in personality, losing interest in doing things and becoming less empathic. At initial assessment at the age of 56, cognitive examination revealed a fluent aphasia with anomia, prosopagnosia and impaired visual memory but with intact verbal memory and executive function. Magnetic resonance imaging (MRI) of the brain demonstrated bilateral but asymmetrical atrophy of the temporal lobes, more prominent on the right side (Fig. 1a). No changes were seen in the primary motor cortex on MRI. She was diagnosed as having a right temporal lobe dominant SD. Her symptoms deteriorated over the next few years with increasing behavioural change, developing obsessive and abnormal eating behaviours by the age of 59, and worsening cognitive impairment.

At the age of 60, she developed weakness of the left hand. This progressed over the next few years such that by the age of 63 she had weakness particularly affecting the left side of the body, and she required the use of a wheelchair. Examination at the time revealed upper motor neurone signs in the upper and lower limbs with increased tone and clonus but without any lower motor neuron features. She died at the age of 65.

At autopsy, the brain weighed 820g before fixation. The left-half brain was examined histologically according to QSBB protocol. No spinal cord was available for examination. Macroscopic examination demonstrated global atrophy with emphasis on the orbitofrontal and temporal cortices (Fig. 1b). The anterior aspect of the temporal lobe was more severely involved. Microscopically, marked loss of neurons with gliosis was noted through the full cortical thickness in the temporal and insular cortices and, to a lesser extent, in the frontal and parietal cortices (Fig. 1c). Although Betz cells were present and not noticeably reduced in number, infiltration of macrophages and gliosis in the motor cortex was seen (Fig. 1d-f). In addition, numerous amoeboid microglial cells were found in the cerebral peduncle (Fig. 1g). There were abundant TDP-43 positive inclusions predominantly forming long corkscrew-shaped threads in the frontal and temporal cortices, corresponding to TDP-43 Type C (Fig. 1h). Fine thread-like TDP-43-positive inclusions were also found in a Betz cell (Fig. 1i). There was no neuronal loss or TDP43 pathology in the hypoglossal nucleus.

We investigated the association of CTD with laterality of temporal lobe atrophy in a further 16 archival cases with TDP-43 type C pathology (supplementary table). Most of the patients including the present case (88.2%, n = 15/17) with TDP-43 type C developed SD. 76.5% of patients (n = 13/17) had moderate to severe microglial pathology in the pyramidal tract assessed with a four-point scale using CD68 immunohistochemistry as reported previously (Supplementary Fig.) [5]. 91.7% of patients (n = 11/12) with CTD showed a predominance of left temporal lobe atrophy based on imaging findings, whilst only the present case had right temporal lobe dominant atrophy, and one did not have sufficient information. Three cases (20%, n = 3/15) had TDP-43 positive inclusions in the hypoglossal nerve nucleus without obvious neuronal loss and two did not have the nucleus represented (case 3, 9 and 10). Spinal cords were available in six of 17 cases, showing preserved neuronal population in the anterior horn but TDP-43 positive intraneuronal inclusions in one case (case 9). Interestingly, only the present case had the combination of a right temporal lobe dominant atrophy and corticospinal tract degeneration.

The present case is an example of CTD and right temporal lobe dominant atrophy in FTLD TDP-43 type C pathology. Due to the involvement of the upper motor neuron system without clinical features of lower motor neuron degeneration, the present case is considered to be FTLD-primary lateral sclerosis (PLS) with predominant TDP-43 type C [6]. Accumulating evidence has suggested that CTD can be found in up to 70% of patients with TDP-43 type C pathology [4, 7, 8]. Kobayashi et al. reported four patients with the clinical diagnosis of SD in whom CTD and FTLD TDP-43 type C pathology were found while lower motor neurons were preserved [7]. In addition, Yokota et al. revealed that three of seven patients with TDP-43 type C and CTD had left side-predominant cerebral atrophy and no case showed right side-predominant atrophy [8]. In keeping with those previously reported, 76.5% of our cases had CTD without obvious loss of lower motor neurons and 91.7% of patients with CTD showed a predominance of left temporal lobe atrophy, confirming a close association between TDP-43 type C pathology, PLS and left-side predominant temporal atrophy. On the other hand, Josephs et al. emphasised that 66% of patients with CTD and TDP-43 type C pathology developed right-sided temporal lobe atrophy when compared with other TDP-43 cases without CTD [4]. In contrast, our present case represents a lone case with right temporal lobe atrophy among 12 cases with TDP-43 type C and CTD. Patients with left side predominant temporal atrophy tend to be referred to neurological departments. At QSBB, most cases are from dementia and movement disorder clinics, therefore there may be a bias towards left-side predominant cases in our cohort. However, our results suggest that unknown factors might contribute to the laterality of temporal lobe atrophy. Recently, Takeuchi et al. have reported that some patients with FTLD-motor neuron disease (MND), characterised typically by both upper and lower motor neuron signs can also develop predominant degeneration of the upper motor neuron system with relatively spared lower motor neurons [9]. These FTLD-MND patients were characterised by a rapid disease progression culminating in death within two years after the onset. Bulbar dysfunction was a common initial symptom. Pathologically, these cases showed numerous TDP-43-positive dot-like dendritic neurites similar to TDP-43 type E pathology [3, 9]. In conclusion, a proportion of FTLD-PLS and FTLD-MND can have distinct clinicopathological phenotypes. The factors that govern these characteristic findings warrant further investigations.

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**Author contributions**

YM, HL, ZJ, TL, and JH designed the study. JR and CM obtained clinical data. SC contributed to the pathological data. YM and JH performed the histopathology assessment. All authors contributed to the interpretation of data and writing the manuscript.

**Conflicts of interest**

None

**Ethical Approval**

We used brain tissue from cases donated to the Queen Square Brain Bank for Neurological Disorders, UCL Queen Square Institute of Neurology. The brain donation programme and

protocols have received ethical approval for donation and research by the NRES Committee London – Central and tissue is stored for research under a license issued by the Human Tissue Authority (No. 12198).

**Figure legend**

**Fig. 1** (a) Magnetic resonance imaging of the brain at the age of 56 demonstrating bilateral atrophy in the temporal lobes, more prominent on the right side. (b) Gross examination revealing severe frontal and temporal lobe atrophy with marked ventricular enlargement. (c) Almost complete loss of neurons with severe gliosis in all cortical layers of the temporal cortex. (d) Mild neuronal loss with preserved Betz cells (arrowheads) in the motor cortex. (e) Proliferation of reactive astrocytes (asterisk) and (f) infiltration of macrophages in the motor cortex (arrows). (g) Numerous amoeboid microglial cells in the cerebral peduncle. (h) Numerous transactivation response DNA-binding protein 43 kDa (TDP-43) positive long corkscrew-shaped threads in the frontal cortex (white arrowheads) and (i) TDP-43 positive thread-like inclusions in a Betz cell (white arrows). Hematoxylin and eosin staining (c, d), glial fibrillary acidic protein (e), CD68 (f, g) and TDP-43 (h, i). Bars = 1 cm in b; 100 μm in c-e; 20 μm in f-i.

**Supplementary Fig.**

Semi-quantitative grading of microglial pathology using a four-point scale. Examples of 1+ (mild) (A), 2+ (moderate) (B) and 3+ (severe) (C). A-C: CD68 immunohistochemistry. Bars = 50 μm.

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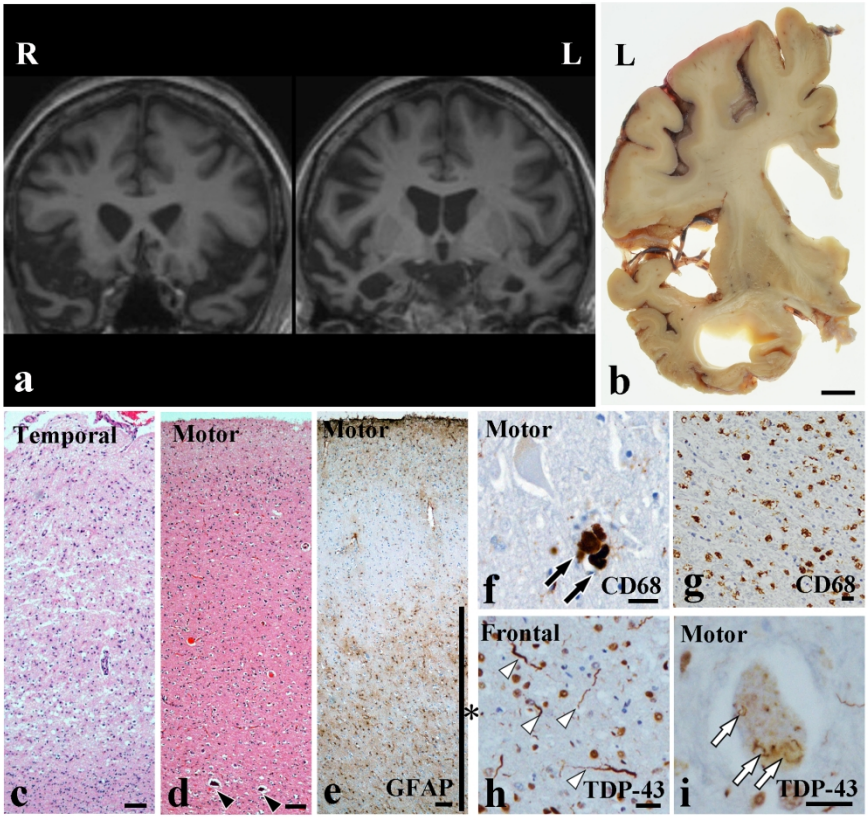


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