Pathological correlates of white matter hyperintensities on cadaveric MRI in progranulin-associated frontotemporal dementia

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Background

- White matter hyperintensities (WMH) are present on MRI brain scans of individuals in healthy aging, or with cerebral small vessel disease, vascular dementia or Alzheimer's disease and are due to white matter damage from ischaemia. WMH are also present in individuals with multiple sclerosis, but due to immune-mediated demyelination, rather than vascular disease.
- WMH are less commonly seen in frontotemporal dementia (FTD), but several studies have reported their presence in individuals with familial FTD due to progranulin (*GRN*) mutations, who lack any vascular risk factors [1-7]. GRN plays a key role in regulating inflammatory pathways [8,9].
- The cause of WMH in FTD is unknown and their histopathological correlates have not previously been studied in detail. However, cadaveric brain MRI (scanning an individual's brain *in situ* within 24 hours of death) enables precise correlation of neuroimaging abnormalities with histology in post-mortem brain tissue [10].
- We hypothesised that WMH in individuals with *GRN* mutation associated FTD are not due to vascular disease, but due to an alternative process linked to GRN haploinsufficiency, leading to demyelination and axonal loss. We investigated the histopathological correlates of WMH in a patient with *GRN*-mutation associated behavioural variant FTD who underwent cadaveric MRI and post-mortem brain tissue analysis.

Clinical details

- **Presentation:**
  - A female patient aged 60 developed progressive behavioural change, episodic memory impairment, dyscalculia and speech disturbance, as well as asymmetrical, extrapyramidal and dystonic limb signs, worse on the right. She was admitted to a nursing home aged 65 and died aged 68. The final clinical diagnosis was behavioural variant FTD. Her brain was donated to the Queen Square Brain Bank for post-mortem analysis.
- **Past history:**
  - Progressive right-sided facial hemi-atrophy diagnosed 15 years prior to cognitive decline. Cough with persistent peripheral eosinophilia, pericardial thickening and pericardial effusion; no cause found after extensive investigation. No vascular risk factors.
  - Family history of dementia: mother developed acute psychosis with delusions aged 65 followed by progressive cognitive decline over 20 years.
- **Investigations:**
  - EEG and cerebrospinal fluid analysis normal. All blood tests normal, except for moderate peripheral eosinophilia 1.11 (range 0-0.4 x 10^9/L) and positive rheumatoid positive particle agglutination test (1/80 titre).
  - DNA analysis on a research basis identified a heterozygous *GRN* Q130fs mutation but no other FTD-associated mutations.

Methods

Imaging

In vivo MRI 2.6 years before death

↓

Cadaveric MRI <24 hours after death

↓

5 brain regions selected for histopathology (Figure 1)

↓

WMH segmentation of cadaveric MRI (Figure 2)

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SPM analysis of atrophy (Figure 3)

Histopathology

Brain tissue fixed, blocked & cut into sections

↓

Routine immunohistochemistry of sections (TDP-43, Aβ, tau, α-synuclein)

↓

Detailed analysis of sections from 5 brain regions (H&E, LFB, Perl stains; SMI31, MBP, GFAP antibodies)

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Assessment of general histological changes → Neuronal loss, Axonal loss, Myelin loss, Spongiosis, Gliosis

↓

Assessment of vascular histological changes → See **Table 1**

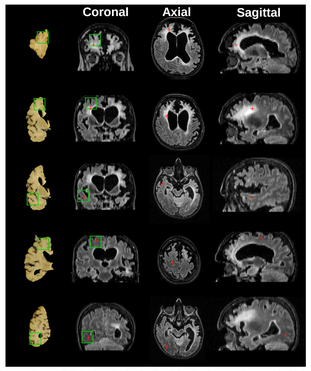

Figure 1 **Comparison of right hemispheric fixed brain tissue slices with FLAIR sequences of cadaveric MRI scan to enable accurate tissue block selection.** Images in far left column show where tissue blocks (green boxes) were obtained from post-mortem brain tissue slices; red crosses = equivalent points across imaging views.

Table 1 **Parameters of vascular pathology were semi-quantitatively assessed in brain regions of interest, using the following scoring system, based on recommendations of the VCING for staging of cerebrovascular pathology in dementia [12]:**

Vascular changes scoring			Vessel wall pathology scoring
Perivascular space dilatation 0 = absent 1 = perivascular space < artery diameter in all sections 2 = perivascular space ≥ artery diameter in the minority of sections 3 = perivascular space ≥ artery diameter in the majority of sections			**Arteriolosclerosis/arteriosclerosis** 0 = normal 1 = mild thickening of the vessel media, mild fibrosis 2 = partial loss of smooth muscle cells in the media, moderate hyaline fibrosis 3 = complete loss of smooth muscle cells in the media, severe hyaline fibrosis, lumen stenosis
Perivascular haemosiderin leakage 0 = absent 1 = <3 haemosiderin granule deposits in the perivascular space 2 = 3-5 haemosiderin granule deposits in the perivascular space 3 = >5 haemosiderin granule deposits in the perivascular space			**Fibrinoid necrosis and microaneurysms** 0 = absent 1 = present
Myelin loss 0 = dense and homogeneous myelin staining 1 = mild diffuse or focal myelin pallor 2 = severe focal/diffuse myelin pallor with vacuolation or tigroid appearance of the white matter 3 = total focal/diffuse destruction of the myelin, or white matter infarcts			**Cerebral amyloid angiopathy** 0 = absent 1= trace or occasional vessels affected 2 = one or a few vessels circumferentially affected 3 = widespread involvement of circumferentially affected vessels 4 = as 3, with secondary changes
Microinfarcts 0 = absent 1 = present	**Large infarcts** 0 = absent 1 = present	**Lacunar infarcts** 0 = absent 1 = solitary 2 = 2-4 3 = 5 or more	
Microhaemorrhages 0 = absent 1 = present			
Larger haemorrhages 0 = absent 1 = present			

Results

- **Imaging:** *In vivo* and cadaveric MRI brain scans showed asymmetric WMH, mostly affecting frontal and parietal lobes, worse on the left (**Figures 1 & 2**). WMH were present predominantly in the middle layers of the frontal lobes, rather than just periventricularly or juxtacortically (**Figure 2**) and matched areas of worst atrophy.
- There was progressive, asymmetric (left worse than right) frontotemporal and parietal atrophy (**Figure 3**) over time on *in vivo* and cadaveric MRI scans.

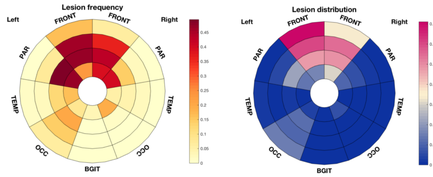

Figure 2 **Bull's-eye schematic of the observed WMH lesion frequency (left diagram) and lesion distribution (right diagram) within different brain regions and layers in the cadaveric MRI brain scan.** Colour scale bars represent the degree of lesion frequency or distribution. Brain regions: FRONT = frontal; PAR = parietal; TEMP = temporal; OCC = occipital; BGIT = basal ganglia and thalami. Central hole = ventricles.

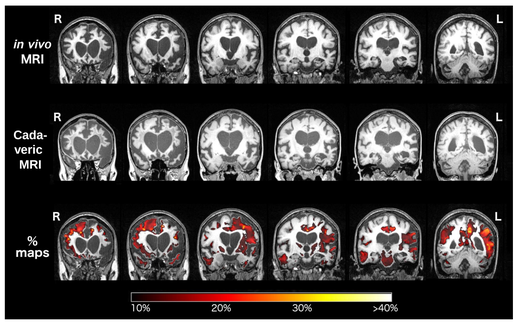

Figure 3 **Coronal sections of the *in vivo* (top row) and post-mortem cadaveric (2nd row) T1-weighted MRI brain scans in the rostro-caudal direction**. The third row shows the longitudinal SPM overlay representing 10% or greater volumetric contraction at the time of death compared with the *in vivo* scan, with corresponding colour bar scale.

- **Pathology:** Frontotemporal lobar degeneration with Type A TDP-43 pathology and no Aβ, tau or α-synuclein.
- **Detailed assessment** of 5 regions: severe spongiosis, neuronal and myelin loss, axonal loss and severe grey and white matter gliosis in right frontal pole (**Figure 4**) and anterior frontal lobe, which both had severe WMH on MRI. Mild or no changes in right occipital lobe which lacked WMH on MRI. Mild to moderate changes in right posterior frontal and right temporal lobes.
- Severity of cortical pathology matched severity of white matter pathology in all regions analysed.
- No or minimal vascular pathology in all 5 regions (even those with severe WMH).

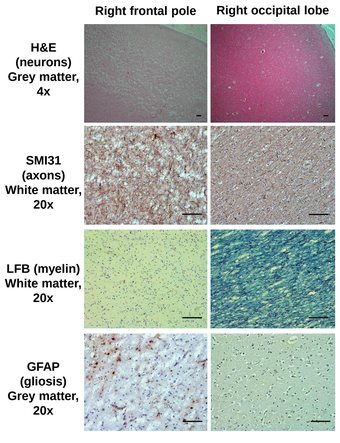

Figure 4 **Severity of histopathological changes across two of the five brain regions assessed.** Examples shown demonstrate changes within the brain region with the most severe WMH (right frontal pole), and absent WMH (right occipital lobe). 4x and 20x = magnification on microscope. H&E = haematoxylin and eosin, SMI31 = antibody labeling phosphorylated neurofilament, LFB = Luxol fast blue, GFAP = glial fibrillary acidic protein. Scale bar = 100μm.

Discussion

- Although WMH have been reported in FTD, particularly in individuals with *GRN* mutations [1-7], this is the first study to characterize their histopathological correlates in detail.
- Our patient had prominent, asymmetrical WMH, predominantly in the frontal and parietal lobes, on both *in vivo* and cadaveric brain MRI, which matched areas of most significant grey matter atrophy.
- Most WMH occurred in the middle layers of both frontal lobes rather than immediately periventricularly or juxtacortically, consistent with a previous study of *GRN* mutation carriers with FTD [6]. This is different from the appearance of WMH in individuals with vascular disease, which tend to be more periventricular in location.
- Our study used careful correlation of cadaveric *in situ* brain MRI appearances with detailed post-mortem histopathological analysis to confirm that vascular pathology was absent or minimal in areas of severe WMH. Alternative mechanisms could include chronic neuroinflammation secondary to GRN haploinsufficiency, or axonal degeneration following cortical neuronal death.
- Future studies should examine for both histopathological and *in vivo* imaging evidence of excess neuroinflammation (for example microglial activation) in individuals with sporadic and familial FTD. They should also assess whether the degree of WMH could be used as a biomarker in both symptomatic and pre-symptomatic *GRN* mutation carriers in future clinical trials.

Key points

- An imaging pattern of asymmetrical WMH on MRI, present predominantly in the middle of the frontal lobes, appears to be a particular feature of FTD with an underlying *GRN* mutation.
- Vascular changes do not underlie these WMH in *GRN*-mutation associated FTD.
- Non-vascular mechanisms such as chronic neuroinflammation could lead to development of WMH in *GRN* mutation carriers.

References & Acknowledgements

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