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 individuals with GRN mutation associated FTD are not due to vascular disease, but due to an alternative process linked to GRN haplosufficiency, 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

- 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.
- Post 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 0.4-0.8 x 109/L) and positive rheumatoid positive particle agglutination test (1/80 titre).
- SVA analysis on a research basis identified a heterozygous GRN G1030A mutation but no other FTD-associated mutations.

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 frontoparietal lobes, on both in vivo and cadaveric brain MRI, which matched areas of most significant grey matter atrophy.
- Most WMH occurred in the midlayers 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 haplosufficiency, 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 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.