Dual pathogenic mutations in SQSTM1 and C9orf72 as a cause of frontotemporal dementia with primary lateral sclerosis

Hanya Benotmane[1], Ione O.C. Woollacott[1], Martina Bocchetta[1], Jonathan D. Rohrer[1]

Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, London, United Kingdom

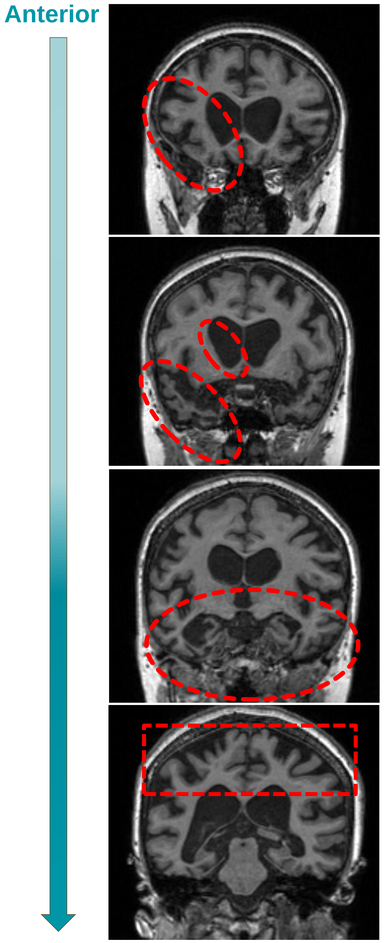
Background

Hexanucleotide repeat expansions in the *C9orf72* gene have been found to be the leading genetic cause of both familial frontotemporal dementia (FTD) and motor neuron disease (MND). However there are a number of other genetic causes of both FTD and MND including, less commonly, mutations in sequestosome 1 (*SQSTM1*) which codes for the cargo protein p62, involved in autophagosomes assembly. Occasionally, people with FTD or MND have been described with dual pathogenic mutations, although this is rare.

Methods

Here we describe the clinical and imaging features of a woman who presented with atypical FTD and motor neurone involvement who was found to carry both a pathogenic *C9orf72* expansion and a deleterious c.1185dup, p.Glu396* heterozygous *SQSTM1* mutation.

Imaging



Volumetric MRI preformed one year after initial examination showed multiple neuroimaging abnormalities as seen here on the left:

- She had bilateral but asymmetrical frontal lobe atrophy, which was more significant on the right, with clear expansion of anterior horns of lateral ventricles.
- There was substantial bilateral caudate nucleus atrophy and anterior temporal lobe atrophy, both worse on the right.
- There is very significant atrophy of the hippocampus, amygdala and superior temporal gyrus, and atrophy of the insula and inferior and medial frontal gyrus.
- She also had widespread cerebral atrophy spreading posteriorly affecting the parietal cortex bilaterally.

Case

Symptoms started at the age of 60 with a change in personality and impaired behaviour. She was apathetic and had reduced verbal fluency and naming difficulties but had intact posterior cortical functions. On initial examination her MMSE score was 27/30. She was initially diagnosed with behavioural variant FTD.

She continued to deteriorate and by the age of 63 developed prosopagnosia with difficulty recognising neighbours. She also had semantic impairment with difficulty naming people and objects with deteriorating spelling and reading. Two neuropsychology assessments 6 months apart demonstrated progressive executive dysfunction, impaired episodic memory, reduced processing speed, and semantic impairment affecting both naming and comprehension

At the age of 66 she developed asymmetrical limb weakness and stiffness, with upper motor neurone features only on examination, suggestive of primary lateral sclerosis (PLS).

She deteriorated rapidly over the next couple of years, although never developed lower motor neurone features when subsequently examined. She died at the age of 69.

Conclusions

The co-presence of both a *SQSTM1* mutation and *C9orf72* expansion is rare. It remains unclear which mutation accounts for which of the features seen. Focal right temporal lobe atrophy is more common with *SQSTM1* mutations, but PLS is uncommon with both mutations. It may be therefore that it is the dual mutations together that explain the altered phenotype.

It is paramount to better understand the roles which *SQSTM1* and *C9orf72* mutations have on cellular pathways and how their combination results in rare phenotypes.

Acknowledgements: The Dementia Research Centre is is an Alzheimer's Research UK co-ordinating centre and has received funding from Alzheimer's Research UK, the Brain Research Trust and the Wolfson Foundation. Part of this work was carried out at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme which supports the NIHR Biomedical Research Unit in Dementia based at UCLH/UCL. HB is supported by the Biomedical Research Centre (BRC). JDR is an MRC Clinician Scientist and has received funding from the NIHR Rare Disease Translational Research Collaboration.