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Brief communication

White matter hyperintensities characterize monogenic frontotemporal dementia with granulin mutations

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ABSTRACT

No study but one has suggested the presence of white matter hyperintensities (WMHs) in frontotemporal dementia (FTD), limited to 4 cases carrying pathogenic *Granulin* (*GRN*) gene mutations. We investigated the presence of WMHs in a cohort of 14 FTD patients with pathogenic *GRN* mutations (GRN+), 28 patients without *GRN* mutations (GRN−) and 18 healthy controls (HC). We further considered 11 asymptomatic GRN+ subjects and 11 young age-matched healthy controls (yHC). The WMH burden was automatically computed and a voxelwise-based analysis was carried out to explore the differences in WMH brain spatial distribution. FTD-GRN+ patients had increased total WMH burden than both HC ($p < 0.001$) and FTD-GRN−($p = 0.01$) groups. WMHs were mainly localized in the right middle frontal and superior temporal gyri, in the left superior frontal in the left parietal gyri. No significant differences of WMH burden between asymptomatic GRN+ and yHC were observed. The presence of WMHs in cases of FTD may suggest a novel mechanism of GRN disease-related neurodegeneration, may be of help in the differential diagnosis, and in guiding genetic screening.

1. Introduction

White matter hyperintensities (WMHs) have been described in neurodegenerative disorders, being associated with dementia risk (Debette and Markus, 2010), and in some cases prompting the diagnostic work-up (Mortamais et al., 2013; Prins and Scheltens, 2015). Pathological findings in regions of WMHs include myelin pallor, tissue rarefaction associated with loss of myelin and axons, and mild gliosis (Debette and Markus, 2010; Fazekas et al., 1993).

Frontotemporal dementia (FTD) is a neurodegenerative disorders mainly characterized by behavioral disturbances, deficits of executive functions and language impairment, frequently occurring in presenile subjects (Rascovsky et al., 2011). In many cases, FTD pathogenesis relies on genetic predisposition (Rademakers et al., 2012), whereas environmental and vascular risk factors have not been found important for the disease onset. One of the most common cause of monogenic FTD is due to mutations within *Granulin* (*GRN*) gene, which cause haploinsufficiency of progranulin, a protein involved in inflammation, tissue repair, and cancer (Toh et al., 2011).

Only 2 previous studies have investigated the presence of WMHs in FTD, describing widespread WM lesions in 4 patients GRN mutation carriers and in a large Italian family, respectively (Caroppo et al., 2014; Pietroboni et al., 2011).

In the present study, we assessed WMHs in patients with FTD, with the attempt to confirm increased load of WM changes in those patients bearing *GRN* mutations, both symptomatic and asymptomatic. If this was confirmed, WMHs should be considered in the assessment of patients with FTD to better characterize the phenotypes and to guide genetic screening.

2. Methods

2.1. Setting and participants

Patients fulfilling criteria for FTD were consecutively recruited from the Centre for Aging Brain and Neurodegenerative

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Disorders, University of Brescia, Italy (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). All subjects underwent somatic and neurologic evaluation, routine laboratory examination, and a complete mental status evaluation. Vascular risk factors were carefully recorded. Patients included in the present study were those with both brain magnetic resonance imaging (MRI) scan and blood sampling. Patients with previous stroke, intracranial mass or normal pressure hydrocephalus documented at MRI, or patients with severe metabolic disorders, that is, diabetes, hypertension, hypercholesterolemia, or hepatic disorders, were excluded by the present study. Each patient underwent genetic screening for *GRN* mutations; patients did not carry even mutations within *microtuble-associated protein tau* (*MAPT*) and *C9orf72* genes. A comprehensive neuropsychological and behavioral assessment was carried out, including FD-modified Clinical dementia Rating scale (FTD-modified CDR), as previously described (Borroni et al., 2010).

A group of healthy controls (HC) were included for neuroimaging comparisons. HC, recruited from patient's relatives or caregivers, had no motor or cognitive complains, had no cognitive or functional disturbances as supported by a brief standardized assessment (Mini-Mental State Examination score $\leq$28/30 and maintained activities of daily living; Folstein et al., 1975; Katz et al., 1963; Lawton and Brody, 1969).

To further assess WMHs in *GRN* disease, we included a group of asymptomatic subjects carrying *GRN* mutations (aGRN+) and a group of young healthy controls (yHC), this latter recruited among siblings of aGRN+ subjects. aGRN+ and yHC were found cognitively healthy on the basis of brief neuropsychological assessment (FTD-modified CDR = 0, Mini-Mental State Examination score $\geq$28/30 and maintained activities of daily living). aGRN+ and yHC were almost 20 years younger than FTD patients' groups.

Informed consent was obtained for blood collection and genetic analyses from each subject. The work was conformed to the Helsinki Declaration and was approved by local Ethic Committee of Brescia Hospital, Italy.

2.2. MRI data acquisition and WMH segmentation

Brain images were collected using a 1.5 T MR scanner (Siemens Avanto, Erlangen, Germany) to acquire 3D MPRAGE T1-weighted scan (repetition time = 2050 ms, echo time = 2.56 ms, matrix = $1 \times 1 \times 1$, in-plane field of view = 256×256 mm^2, slice thickness = 1 mm, flip angle = 15°) and fluid-attenuated inversion recovery (FLAIR) T2-weighted scan (repetition time = 8200 ms, echo time = 104 ms, matrix = 168×320, in-plane field of view = 240 mm, slice thickness = 5 mm, flip angle = 150°).

The WMHs segmentation was computed on T1-weighted and T2 FLAIR images using the Wisconsin White Matter Hyperintensities Segmentation Toolbox version 1.3 (W2HMS; Ithapu et al., 2014) in SPM12b (http://www.fil.ion.ucl.ac.uk/spm). A per-subject summary measure of WMH volume burden (i.e., total WMH; deep WMH; and periventricular WMH) was automatically calculated on the probability map outputs. It represents an unbiased estimator of hyperintensity burden in the form of raw voxel count, adjusted for intracranial volume to account for the differences in brain sizes. Furthermore, WMH burden was also computed subject by subject by the ARWMC Wahlund scale (Wahlund et al., 2001).

2.3. Statistical analysis

The data were analyzed using SPSS 16.0 software (http://www.spss.com). Significant differences of sociodemographic and clinical data were assessed by Mann-Whitney *U* or Kruskal-Wallis and chi square test, as appropriate. The mean value of WMH burden measures and WMH distribution pattern (i.e., total WMH; deep WMH, and periventricular WMH) was calculated for all the included groups, separately, and significant differences between groups were investigated by Mann-Whitney test.

For voxelwise WMH analysis, probability lesion belief maps were normalized to Montreal Neurological Institute space and smoothed with a 12 mm Gaussian kernel. Group differences were evaluated by 2 analysis of covariance model designs: the first considered the 3

Table 1
Demographic characteristics, WMHs burden and percentage brain distribution in FTLD patients and controls

	HC	FTD		*p*-value			yHC	aGRN+	*p*-value
		GRN+	GRN−	GRN+ vs. HC	GRN+ vs. GRN−	GRN− vs. HC			
Demographic characteristics									
N	15	14	28				11	11	
Age at evaluation, years	60.3 ± 12.6	63.8 ± 6.6	65.2 ± 8.1	0.40	0.60	0.49	40.4 ± 9.9	42.0 ± 6.6	0.37
Age at onset, years	—	60.9 ± 7.6	61.6 ± 7.8	—	0.99	—	—	—	—
Gender, M (%)	8 (53)	5 (36)	19 (68)	0.34[a]	0.05[a]	0.35[a]	3 (27.3)	6 (54.5)	0.19[a]
FTD-modified CDR	0.0	5.4 ± 3.8	4.9 ± 3.0	—	0.99	—	0.0	0.0	—
bvFTD, N (%)		7 (50)	14 (50)						
PPA, N (%)		5 (36)	10 (36)						
CBS, N (%)		2 (14)	4 (14)						
WMH burden									
Total WMHs	109.211 ± 159.811	243.669 ± 126.446	134.054 ± 107.282	**0.002**	**0.010**	0.126	96.751 ± 93,057	60.078 ± 41.432	0.85
Deep WMHs	90.213 ± 153.727	205.810 ± 115.378	110.017 ± 97.879	**0.002**	**0.009**	0.120	73.397 ± 81,425	41.732 ± 33.533	0.85
Periventricular WMHs	18.998 ± 9.930	37.859 ± 16.625	24.037 ± 15.347	**0.004**	**0.007**	0.296	23.353 ± 11,761	18.345 ± 8.411	0.37
WMHs distribution[b]									
% of deep WMHs	65 ± 19	82 ± 7	73 ± 18	**0.01**	0.189	0.14	63 ± 18	63 ± 14	0.85
% of periventricular WMHs	35 ± 19	18 ± 7	27 ± 18				37 ± 18	37 ± 14	

p-values denote significance on Mann-Whitney *U* test or Kruskal-Wallis, otherwise specified.The bold font denotes statistically significant values ($p < .05$).
Demographics characteristics results are expressed as numbers or mean ± standard deviation; percentage between brackets. WMH results are expressed as mean raw voxel count (adjusted for intra cranial volume) ± standard deviation.
Key: aGRN, asymptomatic subjects with GRN mutation; bvFTD, behavioral variant of frontotemporal dementia; CBS, corticobasal syndrome; FTD, frontotemporal dementia; FTD-modified CDR, frontotemporal dementia-modified clinical dementia rating scale; FTLD, frontotemporal lobar degeneration; GRN+, patients with *Granulin* gene mutation; GRN−, patients without *Granulin* gene mutation; HC: healthy controls; M, males; N, number; PPA, primary progressive aphasia; WMHs, white matter hyperintensities; yHC, young HC.
[a] Chi square test.
[b] Percentage of total WMHs.