Extensive White Matter Involvement in Patients With Frontotemporal Lobar Degeneration

Think Progranulin

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20% of familial cases of frontotemporal dementias. All cause haploinsufficiency of progranulin, a protein involved in inflammation, tissue repair, and cancer. Carriers of the GRN mutation are characterized by a variable degree of asymmetric brain atrophy, predominantly in the frontal, temporal, and parietal lobes. We describe 4 GRN mutation carriers with remarkable widespread white matter lesions (WML) associated with lobar atrophy shown on magnetic resonance imaging.

Four GRN mutation carriers (age at onset, 56-65 years) presenting with severe WML were selected from 31 GRN mutation carriers who were followed up in our dementia centers. The WML were predominantly in the frontal and parietal lobes and were mostly confluent, affecting the periventricular subcortical white matter and U-fibers. In all patients, common vascular, metabolic, inflammatory, dysimmune, and mitochondrial disorders were excluded and none had severe vascular risk factors.

Our data suggest that white matter involvement may be linked to progranulin pathological processes in a subset of GRN mutation carriers. The plasma progranulin measurement, which is predictive of GRN mutations, and GRN sequencing should thus be included in investigations of patients with frontotemporal lobar degenerations who show unusual white matter hyperintensities and atrophy on magnetic resonance imaging.

We describe 4 GRN mutation carriers who presented with severe WML, selected from 31 GRN mutation carriers followed up in our dementia referral centers. All patients signed an informed consent form for genetic study that was approved by the ethics committee of Assistance Publique Hôpitaux de Paris.

Case 1
This patient (family 1) did not have any vascular risk factors except for chronic smoking. He had a family history of dementia (Figure 1, F1). At 63 years of age, he presented with apathy, loss of moral sense, excessive spending, and changes in eating habits (Table). Findings from a neuropsychological examination revealed a dysexecutive syndrome. A clinical diagno-
sis of behavioral variants of frontotemporal dementia was made. Magnetic resonance imaging (MRI) of the brain at 66 years of age revealed asymmetrical atrophy in the frontal and parietal lobes. Images of T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences showed bilateral diffuse and confluent WML affecting the periventricular subcortical white matter and U-fibers that were hypointense on T1-weighted sequences. Images of diffusion sequences were negative for acute vascular events (Figure 2). Results of laboratory testing of blood specimens were within the reference ranges (levels of cholesterol, glycemia, angiotensin-converting enzyme, homocysteine, anticardiolipin, anti-β2-glycoprotein 1, anti-DNA, antinuclear antibodies, human immunodeficiency virus and syphilis serologies, arylsulfatase A, hexosaminidases, very-long-chain fatty acid, ceruloplasmin, lactic acid, and pyruvate). Mutations in CSF1R (OMIM 164770) were excluded by gene sequencing. The plasma progranulin level was low (24 ng/mL; reference range, >100 ng/mL; eMethods

Patients affected by dementia are represented in black. Deceased patients are indicated with a bar. Individuals are represented by a diamond for confidentiality. F1 indicates family 1; F2, family 2; F3, family 3.

Table. Clinical and Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, y</td>
<td>63</td>
<td>56</td>
<td>65</td>
<td>56</td>
</tr>
<tr>
<td>Duration of disease, y</td>
<td>...</td>
<td>4</td>
<td>7</td>
<td>...</td>
</tr>
<tr>
<td>Age at death, y</td>
<td>...</td>
<td>70</td>
<td>72</td>
<td>...</td>
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<tr>
<td>Clinical diagnosis</td>
<td>bvFTD</td>
<td>CBDS</td>
<td>bvFTD</td>
<td>bvFTD and amnestic syndrome</td>
</tr>
<tr>
<td>Symptoms at onset</td>
<td>Apathy, hyperphagia, disinhibition</td>
<td>Apathy, indifference, hyperphagia</td>
<td>Apathy, affective indifference</td>
<td>Memory deficit</td>
</tr>
<tr>
<td>Behavior and frontal signs</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Apathy and/or inertia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Hyperorality</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Emotional state</td>
<td>Emotional lability</td>
<td>Indifference</td>
<td>Indifference</td>
<td>Indifference</td>
</tr>
<tr>
<td>Dysexecutive syndrome</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Archaic reflexes</td>
<td>Bilateral grasping</td>
<td>Bilateral grasping</td>
<td>Bilateral grasping, prehension and utilization behavior</td>
<td>Prehension behavior</td>
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<tr>
<td>Parkinsonism</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Rigidity</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Akinesia</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tremor</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
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<tr>
<td>Apraxia</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Dystonia</td>
<td>−</td>
<td>Upper limb and facial dystonia</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>SPECT/PET findings</td>
<td>Predominantly right frontotemporal hypometabolism</td>
<td>Severe frontoparietal hypoperfusion</td>
<td>Severe frontal, perisylvian, hippocampal, and moderate parietotemporal hypoperfusion</td>
<td>Predominantly left hippocampal and prefrontal hypoperfusion</td>
</tr>
</tbody>
</table>

Abbreviations: bvFTD, behavioral variant of frontotemporal dementia; CBDS, corticobasal degeneration syndrome; PET, positron emission tomography; SPECT, single-photon emission computed tomography; +, present; −, absent.

**Case 2**
The patient (family 2) had a history of elevated blood pressure (maximum, 160/100 mm Hg) that was well controlled with angiotensin-converting enzyme–inhibitor therapy. He had no other vascular risk factors or migraine. He had a family history of FTLD (Figure 1, F2). He presented with behavioral disorders and a frontal cognitive syndrome at 56 years of age. At 66 years, he developed akinetic-rigid parkinsonism, facial and upper-limb dystonia, gestural apraxia, and left neglect. Corticobasal degeneration syndrome was diagnosed. At 57 years, MRI of the brain revealed bilateral frontal, temporal, and to a lesser extent, parietal atrophy. Images of T2-weighted and FLAIR sequences also showed bilateral extensive frontal and parietal hyperintensities affecting the periventricular subcortical white matter and U-fibers that were hypointense on T1-weighted sequences (Figure 2) but not contrast enhanced. The cerebrospinal fluid was acellular, and polymerase chain reaction for John Cunningham virus in the cerebrospinal fluid was negative. Results of laboratory testing of the blood specimens were within the reference ranges (levels of arylsulfatase A, ceruloplasmin, lactic acid, very-long-chain fatty acid, and human immunodeficiency virus and syphilis serologies). Results of electromyogram and muscle biopsy with periodic acid-Schiff, cytochrome oxidase, nicotinamide adenine dinucleotide, and succinate dehydrogenase activity measurements were normal. No ragged red fibers or mitochondrial alterations were present. Genetic sequencing of NOTCH3 (OMIM 600276) and CSF1R and results of skin biopsy were normal. A c.1494_1498delAGTGG, p.Glu498Aspfs*12 mutation was identified in the GRN gene. Patient 2 died at 70 years of age. Postmortem examination of the brain could not be performed.
Case 3
The patient (family 3) had no vascular risk factors. He had a family history of FTLD (Figure 1, F3). He developed apathy, social withdrawal, indifference, overspending, and bulimia at 65 years of age (Table), suggesting a behavioral variant of frontotemporal dementia. Neuropsychological test results revealed a dysexecutive syndrome. He secondarily developed lower-limb akinetic-rigid parkinsonism, and he became mute at 70 years of age. He died at 72 years. An MRI of the brain at 70 years revealed marked bilateral frontotemporal atrophy. Images of T2-weighted and FLAIR sequences showed bilateral patchy and confluent subcortical and periventricular white matter hyperintensities that predominated in the frontal and parietal lobes. These lesions were hypointense on T1-weighted sequences (Figure 2). No CSF1R mutations were found. Sequencing of GRN revealed a c.813_816delCACT, p.Tyr272Serfs*10 mutation.

Case 4
The patient (family 3) was the brother of the patient described in case 3. He had no vascular risk factors. He presented with episodic memory disorder at 56 years of age. He later developed stereotyped behaviors, loss of control, apathy, and upper-limb akinetic-rigid parkinsonism (Table). Neuropsychological evaluation revealed moderate frontal executive dysfunction and verbal memory deficit. An MRI of the brain at 59 years of age showed predominantly left cortical atrophy of frontal temporal lobes and left hippocampus. Images of T2-weighted and FLAIR sequences showed extensive WML in the semioval centers and periventricular regions, especially in the anterior frontal lobe. The diffusion-weighted images did not show hyperintensities (Figure 2). After 4 years, the WML had become more extensive, with diffuse frontal parietal and temporal region involvement. Mutations in CSF1R were excluded by gene sequencing. The plasma progranulin level was low (36 ng/mL). He carried the c.813_816delCACT, p.Tyr272Serfs*10 mutation.

Discussion
We describe 4 GRN mutation carriers who showed remarkable widespread and homogeneous white matter involvement on MRI of the brain, without severe vascular risk factors or other white matter diseases, strongly suggesting that these lesions could be indicative of this genotype. In all patients, the lesions affected the periventricular subcortical white matter and U-fibers, were mostly confluent, and predominantly involved the frontal and parietal lobes corresponding to the areas in which atrophy was more marked. The lesions were remarkably severe and much more extensive than lesions occasionally seen in patients with dementia who have cortical atrophy.4 The brainstem, corpus callosum, and cerebellum were spared. No lacunar infarcts were present. Normal diffusion sequences on imaging excluded acute vascular and inflammatory components.

The most common diagnoses to consider in adults with familial dementia associated with extensive WML are hereditary diffuse leukoencephalopathy with spheroid or pigmented orthochromic leukodystrophy and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.5,6 Hereditary diffuse leukoencephalopathy with spheroid and pigmented orthochromic leukodystrophy are rare allelic variants caused by CSF1R mutations. The clinical presentation may be limited to frontotemporal dementia associated with predominantly frontal WML, which is similar to that in our patients.5 Lesions of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy involve the anterior temporal and periventricular white matter and the external capsule and are associated with lacunar infarcts and microbleeds; thus, they are different from our patients.6 These genetic disorders were excluded by molecular analyses. Exceptionally, WML are associated with PSEN1 mutations, but the phenotype is usually that of Alzheimer disease. Peduncular, cerebellar, and callosal lesions, evocative of fragile X-associated tremor/ataxia syndrome, cerebrotendinous xanthomatosis, and Niemann-Pick disease type C, were absent. Other metabolic and mitochondrial disorders (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; Krabbe disease; adrenoleukodystrophy; and metachromatic leukodystrophy) were excluded by specific investigations. Finally, the absence of severe vascular risk factors, and the absence of microbleeds in the deep gray nuclei and brainstem, excluded vasculopathy and cerebral amyloid angiopathy in our patients.

The expression of progranulin, not only in neurons and activated microglia, but also in astrocytes and oligodendroglia,7 suggests that the white matter involvement observed in our patients could be a consequence of progranulin deficiency. Descriptions of other patients with GRN mutations who show similar subcortical white matter signal changes on standard MRI8-11 or white matter damage on diffusion tensor imaging12,13 support this hypothesis. The significance of these lesions and their relationship with progranulin deficiency remain to be understood. White matter was not well evaluated in postmortem studies of GRN mutation carriers, which generally focused on the description of cortical lesions, neuronal loss, and transactive response DNA binding protein 43-positive neuronal inclusions.14 Interestingly, multifocal demyelination resembling multiple sclerosis lesions14 and microglial activation that correlated with white matter intensities detected on standard MRI15 have been described in 3 GRN mutation carriers. In addition, transactive response DNA binding protein 43 inclusions in oligodendrocytes have been detected in GRN mutation carriers.15 Our study demonstrates that WML can be more extensive than previously reported (case 1) and supports the hypothesis of a specific vulnerability of white matter in the GRN genotype.

Conclusions
Previously, neuroimaging studies have shown that the topography of brain atrophy is frequently asymmetric, predominantly involves the frontal, temporal, and parietal cortex in GRN mutation carriers, and can help differentiate GRN carriers from persons with other genetic forms of FTLD.3 More
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importantly, our study shows that, in addition to the pattern of atrophy, the presence of WML could also suggest GRN mutations. In clinical practice, the identification of such extensive lesions in patients with FTLD should thus be included in GRN analysis. Clinical phenotypes are highly variable in GRN mutation carriers, potentially reflecting the influence of genetic or environmental modifiers, and WML might be part of this heterogeneity. Plasma progranulin measurement, which is easy and a more cost-effective assay than genetic sequencing,16 should thus be included in diagnostic investigations of patients presenting with FTLD and uncommon white matter hyperintensities associated with lobar atrophy.

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REFERENCES