

Clinical/Scientific Notes

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FAMILIAL STRIATAL DEGENERATION: NEW MUTATION AND NEUROIMAGING CLUES

Autosomal dominant striatal degeneration (ADSD) (MIM 609161) is a rare genetic disease caused by mutation in the *PDE8B* gene.^{1,2} The disease, with onset in the fourth to fifth decade, is characterized by slowly progressive dysarthria, mild parkinsonism but no tremor, brisk deep tendon reflexes, poor response to levodopa treatment, and distinctive brain MRI findings.^{1,2} Heterozygous mutations in the *PDE8B* gene, first identified in a German family,² result in loss of protein cyclic nucleotide phosphodiesterase (PDE) function. PDEs are responsible for the breakdown of cyclic nucleotides, cyclic adenosine monophosphate, and cyclic guanosine monophosphate, and play a major role in striatal neuron regulation.³ The PDE superfamily consists of 11 families (PDE1–PDE11), each of which has 1 to 4 subtypes. Some neuropsychiatric and neurodegenerative diseases, including depression, schizophrenia, Parkinson disease, Alzheimer disease, and Huntington disease, have changes in phosphodiesterase expression in the brain.³ *PDE8B* expression is higher in specific brain regions affected by ADSD (putamen, caudate nucleus, and nucleus accumbens), producing peculiar lesions in the striatum.^{2,3}

Case report. A 60-year-old woman, from Portuguese ancestry and with previous unremarkable medical history, complained of progressive slowness of movements and slurred speech for the past 2 years. Her deceased mother and brother had been diagnosed with parkinsonism. Neurologic examination disclosed mild bradykinesia, more prominent on the right side of the body, dysarthria, and brisk deep tendon reflexes. She had normal gait and balance. Brain MRI depicted symmetric lesions of the striatum characterized by increased signal on T2-weighted images and low signal on T1-weighted images. The putaminal lesion showed a marked anteroposterior gradient, characterized by a relative sparing of its anterior third and severe damage of its most caudal portion, which assumed a cystic appearance, determining mass effect. The nucleus accumbens, as well as the most medial portion of the caudate head, were also affected. The medial body of the caudate and the connection bundles between the putamen and the caudate nucleus also displayed abnormal signal.

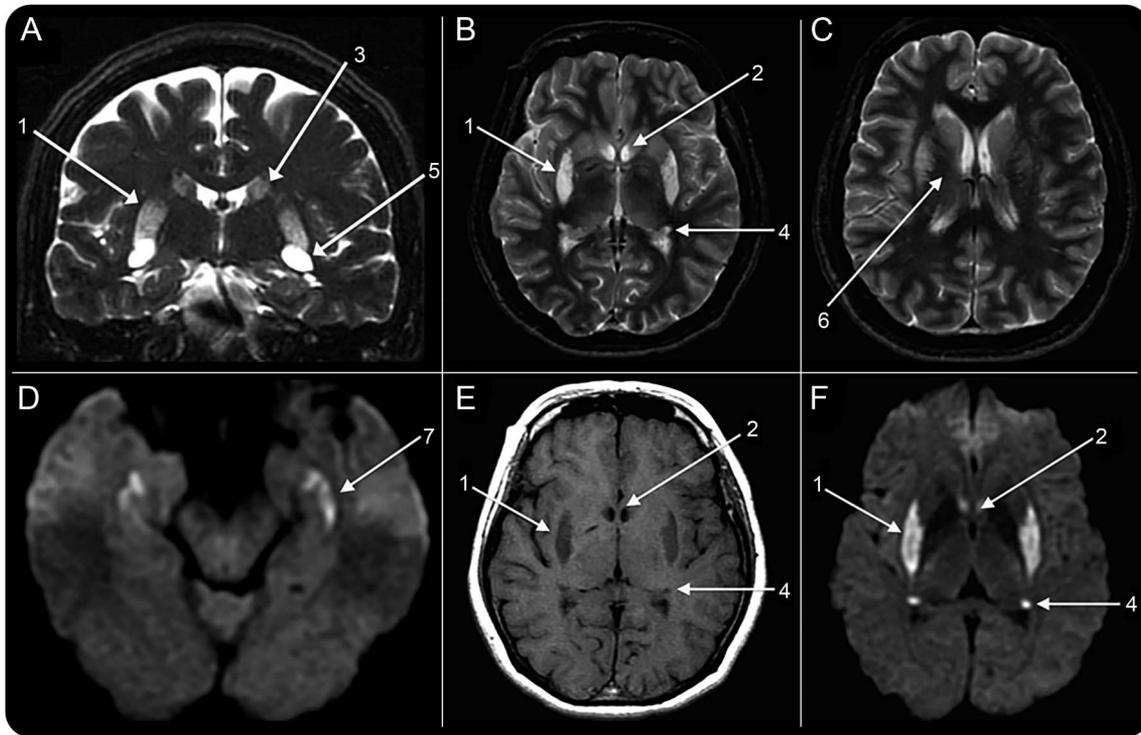
Bilateral restricted diffusion was demonstrated in the dorsal aspect of the putamen, nucleus accumbens, caudate medial body, and tail, as well as in the hippocampus (figure 1). There was no gadolinium enhancement, hemorrhage, or mineral deposition. Blood tests, including renal, hepatic, ceruloplasmin, thyroid, and parathyroid hormones, and CSF analysis were normal. Levodopa 600 mg daily was prescribed but no improvement was observed.

Considering the possible family history of parkinsonism and typical features on brain MRI, particularly nucleus accumbens involvement, genetic testing for the *PDE8B* gene was requested. ADSD was confirmed by genetic analysis, which detected a novel heterozygous mutation in exon 1 of the *PDE8B* gene (c.79delCp. Arg27alafs*38). This creates a shift in the reading frame starting at codon Arg27. The new reading frame ends in a stop codon 37 positions downstream (figure e-1 on the *Neurology*[®] Web site at Neurology.org). To date, this mutation has not been listed in the NCBI dbSNP database. Other family members were not available for genetic testing. Although we did not perform reverse transcription PCR assay, it is a consensus that a stop codon variation can often be assumed to disrupt gene function by leading to absence of the gene product by lack of transcription or nonsense-mediated decay of an altered transcript. Nonsense-mediated decay is an evolutionarily conserved mRNA quality control system in all eukaryotes that degrades transcripts containing premature termination codons. Therefore, the variation found should be considered pathogenic according to the new recommendations.

Discussion. In this report, the MRI abnormalities conform with the typical imaging pattern described in ADSD, distinguished by selective symmetrical striatal lesions (putamen, caudate nucleus, and nucleus accumbens), displaying an anteroposterior gradient in the putamen. The globus pallidi and the thalami characteristically are not involved.

Diffusion changes have not been reported in ADSD. The remarkable imaging changes observed in our patient have unknown mechanism. However, the presence of restricted diffusion might be related to other mechanisms, such as excitotoxicity or cytotoxic edema. Different from previous reports, this patient presented bilateral lesions of the caudate tails with hippocampi

Supplemental data
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Coronal T2-weighted (A) and axial T2-weighted (B, C) brain MRI disclose symmetric bilateral hyperintense signal in the posterior 2/3 of the putamen (1), as well as in the nucleus accumbens (2) and in the medial body (3) and tail (4) of the caudate nucleus. The most caudal portion of the putamen (5) is strikingly affected, displaying mass effect. The connection bundles between the putamen and the caudate nucleus (6) are also affected. (E) Axial T1-weighted image shows decreased signal in the affected areas. (D) Diffusion-weighted imaging shows bilateral symmetrical restricted diffusion in the hippocampus (7). (F) Diffusion-weighted imaging also shows bilateral symmetrical restricted diffusion in the dorsal portion of the posterior 2/3 of the putamen (1), nucleus accumbens (2), and tail of the caudate nucleus (4).

extension. The reason for this abnormal imaging pattern is unknown.^{4,5} Hyperammonemia, hypoglycemia, hypoxic ischemic encephalopathy, mitochondrial disorders, prion disease, Epstein-Barr encephalitis, and autoimmune encephalopathies must be considered as the main differential diagnoses for this imaging pattern.^{6,7}

In patients with mild to moderate parkinsonism with positive family history and marked basal ganglia lesions, particularly with nucleus accumbens involvement, ADSD should be strongly considered and *PDE8B* gene testing requested. As for therapeutic prospective, normalizing cyclic nucleotide signaling via PDE inhibition is a possible target for the treatment of neurodegenerative disorders such as ADSD.

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case report project execution, manuscript review and critique. S. Raskin: genetic evaluation, manuscript review and critique. R.H. Nunes: case report project conception, case report project organization, case report project execution, imaging project, writing of the first draft, manuscript review and critique. A.J. da Rocha: case report project conception, case report project organization, case report project execution, imaging project, writing of the first draft, manuscript review and critique. J.L. Pedroso: case report project conception, case report project organization, case report project execution, imaging project, writing of the first draft, manuscript review and critique.

Study funding: No targeted funding reported.

Disclosure: The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received March 31, 2015. Accepted in final form July 20, 2015.

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Neurology®

Familial striatal degeneration: New mutation and neuroimaging clues
Orlando Graziani Povoas Barsottini, Pedro de Miranda Martins, Hsin Fen Chien, et al.
Neurology published online October 16, 2015
DOI 10.1212/WNL.0000000000002128

This information is current as of October 16, 2015

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