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Neurology 2011;76;301-303
DOI 10.1212/WNL.0b013e318207b01e

This information is current as of January 17, 2011

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http://www.neurology.org/content/76/3/301.full.html

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MUTATIONS IN THE GLUCOCEREBROSIDASE GENE CONFER A RISK FOR PARKINSON DISEASE IN NORTH AFRICA

Heterozygous mutations in the glucocerebrosidase gene (GBA) encoding the enzyme deficient in Gaucher disease (GD), an autosomal recessive lysosomal storage disease, are the most common risk factors for parkinsonism in several populations. A large meta-analysis, pooling genotyping data for the most common mutations from 16 different centers in the United States, Europe, Israel, and Asia, yielded a combined odds ratio (OR) for GBA mutations in subjects with Parkinson disease (PD) of >5 but did not include North Africans. Ashkenazi Jewish patients with PD had the highest mutation frequency (~20%) (controls, 3%). The common LRRK2 G2019S mutation was also very frequent in Ashkenazi Jews (familial, 28%; isolated, 10%). This mutation, on the same haplotype, was also frequent in North African patients with PD (familial, 36%; isolated, 39%), who might, therefore, also have a high frequency of GBA mutations, although GBA mutations were not a risk factor for PD in Tunisian Berber Arabs.

Methods. We studied 194 unrelated patients with PD as reported previously and 177 ethnically matched control subjects, all of North African ancestry. Most patients were from Algeria (n = 147), Morocco (n = 23), Tunisia (n = 14), and Libya (n = 1), and 9 were of unknown origin. Mean ± SD age at onset was 50.9 ± 12.9 years (range 12–78 years), mean age at examination was 58.8 ± 13.3 years (range 14–83 years), mean disease duration was 7.5 ± 5.9 years (range 0–35 years), 52% were men, and 48% reported family histories of PD or were consanguineous. Control subjects, without signs and family histories of parkinsonism, were mostly from Algeria (n = 95) and Morocco (n = 46); their mean age at examination was 49.5 ± 14.5 years (range 19–84 years) and 39% were men. Local ethics committees approved the study.

Peripheral blood samples were collected from each participant with written informed consent. DNA was extracted from leukocytes by standard procedures.

All patients with PD and control subjects were screened for LRRK2 G2019S; most were reported elsewhere. The coding regions of GBA were sequenced completely in all participants (table e-1 on the Neurology® Web site at www.neurology.org). Carrier frequencies in patients with PD and control subjects were compared with the Fisher exact test; statistical significance was defined as p < 0.05 using a one-tailed test. Qualitative and quantitative variables were compared among groups of patients with PD with the Fisher exact test or the nonparametric Kruskal-Wallis test.

Results. Three previously characterized heterozygous GBA mutations [K(−27)R, R131C, N370S], 1 homozygous R131C mutation, and 2 complex alleles [L444P/E326K, RecNciI (A456P/V460V/L444P)] were identified in 9 patients with PD (4.6%) (table 1). One control subject had a rare heterozygous D443N variant of undetermined pathogenicity. Mutation carrier frequency was higher in patients with PD (9 of 194, 4.6%) than in control subjects (1 of 177, 0.5%; p = 0.01; OR = 8.56; 95% confidence interval [CI] = 1.07–68.27). Of the 194 patients with PD, 83 were homozygous or heterozygous for the LRRK2 G2019S mutation (carrier frequency, 42.8%; mean age at onset, 50.2 ± 11.8 years; range 28–74 years), 3 of whom also carried either the GBA L444P/E326K (n = 1) or the K(−27)R allele (n = 2). In addition, 2 probably nonpathogenic variants, E326K and T369M, were found in both patients and control subjects. Although our sample of patients with GBA mutations was small, there were no intergroup clinical differences among GBA mutation carriers, G2019S mutation carriers, and noncarriers, except for the previously reported association of dyskinesias with LRRK2 G2019S (p < 0.001) (table e-2). GBA mutation carriers did not differ from noncarriers with regard to the age at disease onset, but a slightly greater association was observed for patients with PD with an age at onset ≥50 years (5 of 86, 5.8%) compared with that for younger control subjects (age at examination ≤50 years) (0 of 83, p = 0.03).

Discussion. GBA mutations were more frequent in patients of North African origin with PD (4.6%) than in ethnically matched control subjects (0.5%) (p = 0.01; OR = 8.56; 95% CI = 1.07–68.27); the
association was stronger in younger subjects. In contrast, a recent study failed to identify an association between GBA variants and PD in Tunisian Berber Arabs, although these authors might have missed rare GBA variants, because they initially sequenced only a few patients with PD and subsequently looked for only the 2 variants they detected plus the common N370S mutation. The mutation spectrum was similar to that in Tunisian patients with GD: the GBA N370S, L444P, and L444P/R144C mutations account for 74% of all GD alleles identified. Interestingly, the rare K(–27)R allele found in 2 of our patients was the most frequent mutation in the Tunisian PD group.

Of the 194 patients with PD, 42.8% carried the LRRK2 G2019S mutation, 3 of whom also harbored the GBA variants. Their age at onset was similar to that of carriers with single LRRK2 mutations (34–64 years), suggesting that there was no genetic interaction between GBA and LRRK2. However, unlike Ashkenazi Jews, the GBA mutation frequency was much lower than that of LRRK2 G2019S.

Table 1

<table>
<thead>
<tr>
<th>Variants</th>
<th>Patients with PD (age at onset, y, FH status, origin) (n = 194)</th>
<th>Control subjects (age at examination, y, origin) (n = 177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K(–27)R</td>
<td>Het (36, Spo, Algerian)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Het (41, FH, unknown)</td>
<td>0</td>
</tr>
<tr>
<td>R131C</td>
<td>Het (38, Spo, Algerian)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hom (41, Spo, Moroccan)</td>
<td>0</td>
</tr>
<tr>
<td>N370S</td>
<td>Het (50, Spo, Moroccan)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Het (56, Spo, Algerian)</td>
<td>0</td>
</tr>
<tr>
<td>D443N</td>
<td>0</td>
<td>Het (57, Moroccan)</td>
</tr>
<tr>
<td>L444P/E326K</td>
<td>Complex allele (34, *Spo, Algerian)</td>
<td>0</td>
</tr>
<tr>
<td>RecNcil</td>
<td>Complex allele (61, FH, Algerian)</td>
<td>0</td>
</tr>
<tr>
<td>(A456P/V460V/L444P)</td>
<td>Complex allele (69, Spo, Algerian)</td>
<td>0</td>
</tr>
<tr>
<td>E326K</td>
<td>Het (47, FH, Algerian)</td>
<td>Het (44, Algerian)</td>
</tr>
<tr>
<td>T369M</td>
<td>Het (12, Spo, Algerian)</td>
<td>Het (42, Algerian)</td>
</tr>
<tr>
<td></td>
<td>Het (28, Spo, Algerian)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: FH = family history of Parkinson disease; Het = heterozygote; Hom = homozygote; PD = Parkinson disease; Spo = sporadic case.

* These patients had both the LRRK2 G2019S and GBA mutations.

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This case report provides Class IV evidence that thymectomy for a thymoma resulted in resolution of PERM.

**Case report.** On September 15, 2008, a 49-year-old farmer without significant medical history developed pain in his right leg, which became intolerable within 5 days. Lumbosacral spine MRI was normal. He then developed involuntary, painful extension spasms of the right leg, left arm stiffness, speech and swallowing difficulties, intermittent diplopia, dry mouth, constipation, urinary retention, and excessive sweating. He could no longer fully open his mouth, and was referred to our hospital with a tentative diagnosis of tetanus, 8 days after onset.

On admission, he was severely agitated and screaming in pain. He was tachypneic, tachycardic, and sweating profusely. He was unable to stand or sit. There was trismus, dysarthria, rigidity of the left arm and right leg, painful tonic spasms in the right quadriceps, and generalized, nonrhythmic myoclonic jerks, which were triggered by sudden noise or touch but also occurred spontaneously. Neurologic examination was otherwise normal. His tetanus vaccination status was confirmed and partially relieved the painful spasms. The patient was hospitalized in the intensive care unit, but his condition deteriorated. He became confused and the patient’s rapidly progressive rigid-myoclonus (PERM) was probably related to stiff-person syndrome (SPS). In both conditions, most patients have anti-glutamic acid decarboxylase (anti-GAD) antibodies, and both can be paraneoplastic. However, PERM differs from SPS by the presence of brainstem and long tract signs and its aggressive course. Initially, PERM was considered as uniformly fatal. More recently, partial improvement of PERM has been reported in rare cases.1,4 We describe a patient with PERM and glycine receptor antibodies who completely recovered after resection of a thymoma.

**Classification of evidence.** This case report provides Class IV evidence that thymectomy for a thymoma resulted in resolution of PERM.

**Discussion.** The patient’s rapidly progressive rigidity, painful muscle spasms, brainstem myoclonus and other brainstem signs, dysautonomia, and inflammatory CSF changes were consistent with PERM. The muscle recruitment pattern was consistent with brainstem myoclonus (figure, A). Toxicologic analysis showed no evidence of strychnine poisoning. CT of the thorax revealed an anterior mediastinal mass, suggestive of a thymoma (figure, B).

Diazepam and baclofen were started on admission and partially relieved the painful spasms. The patient was hospitalized in the intensive care unit, but his condition deteriorated. He became confused and the patient worsened (video 1 on the Neurology® Web site at www.neurology.org). He received plasma exchange from September 26 to October 6, without clear effect. On October 13, an extended thymectomy was performed. Pathologic examination identified the mass as a cortical, lymphocyte-rich thymoma (thymoma type B1). Methylprednisolone was started postoperatively (100 mg daily), tapered to 4 mg daily over 5 months, and stopped in March 2009. His condition improved dramatically in the first few months after thymectomy. In June 2009, 3 months after cessation of methylprednisolone, diazepam, and baclofen, neurologic examination was completely normal. At the time of manuscript submission (July 2010), the patient remains free of neurologic symptoms (video 2) and is farming at his predisease level.
the acute phase (October 7, 2008) using a cell-based assay. The sample was clearly positive, even though taken shortly after plasma exchange. This is only the second PERM case report with glycine receptor antibodies. The diagnostic value of these antibodies is currently being investigated in larger cohorts of patients with PERM and related disorders.

An association of PERM with thymoma has not been described before, and there have been no previous reports of complete restitution ad integrum of patients with PERM. The chronology suggests that the thymectomy played a major role in the recovery, although the plasma exchange and corticosteroids may also have contributed. Patients with PERM should be carefully screened for thymoma. It will be important to determine how consistently patients with PERM with an associated thymoma recover after thymectomy.

From the Departments of Neurology (K.C., T.B., M.S., W.V.), Radiology (J.V.), and Pathology (T.T.), University Hospitals Leuven, Leuven, Belgium; and Department of Clinical Neurology (M.I.L., A.V.), University of Oxford, Oxford, UK.

Disclosure: Dr. Clerinx, Dr. Breban, and Dr. Schnoeten report no disclosures. Dr. Leite receives research support from the Oxford Biomedical Research Centre, the National Commissioning Group, and the Sir Halley Stewart Trust, UK. Dr. Vincent has served on scientific advisory boards for the Patrick Berthoud Trust and the Myasthenia Gravis Foundation of America; has received funding for travel and a speaker honorarium from Baxter International Inc.; serves as an Associate Editor for Brain; receives royalties from the publication of Clinical Neuroimmunology (Blackwell Publishing, 2005); receives research support from the European Union, NIHR Biomedical Research Centre Oxford, and Sir Halley Stewart Trust; and has received MusK antibody royalties and consulting fees from Athena Diagnostics, Inc., and MusK antibody royalties from RSR Ltd., Cardiff, UK. The University of Oxford, where A.V. is based, receives royalties and payments for antibody assays in neurologic diseases. Dr. Verschakelen, Dr. Tousseyn, and Dr. Vandenberghe report no disclosures.

Received March 9, 2010. Accepted in final form July 28, 2010.

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ACKNOWLEDGMENT

W.V. is a Senior Clinical Investigator of the Fund for Scientific Research—Flanders (FWO).


Figure EMG and CT findings

(A) Rectified surface EMG recordings from the right masseter, sternocleidomastoid, deltoid (pars media), and rectus femoris during a spontaneous myoclonic jerk. Muscle activation starts in the sternocleidomastoid and then spreads rostrally (masseter) and caudally (deltoid and rectus femoris). The vertical line indicates the onset of EMG activity in the sternocleidomastoid. The gray blocks below the masseter, deltoid, and rectus femoris traces indicate the latencies between the onset of activation of the sternocleidomastoid and the respective muscle. (B) CT of the thorax shows an anterior mediastinal mass (arrow).
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