The sample sizes in this study were too small to demonstrate a significant difference in PLPH frequency between the 2 cohorts. Assuming a PLPH frequency that was observed in the 2 patient cohorts in this study, the estimated sample size to show significance for 2-sample comparison of proportions with an α of .05 (2-sided) and a power of 0.90 would be 256 patients per sample.

Olaf Stuve, MD, PhD
Peta D. Cravens, PhD
Mahendra P. Singh, PhD
Elliot M. Frohman, MD, PhD
J. Theodore Phillips, MD, PhD
Gina Remington, RN, BSN
Wei Hu, MD, PhD
Bernhard Hemmer, MD
Michael J. Olek, DO
Nancy L. Monson, PhD
Michael K. Racke, MD

Correspondence: Dr Stuve, Department of Neurology, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75390-9036 (olaf.stuve@utsouthwestern.edu).


Financial Disclosure: None reported. Although the AFFIRM monotherapy trial and the SENTINEL add-on trial with interferon beta-1a (Avonex) were sponsored by Biogen Idec Inc and Elan Corp, the manufacturers of natalizumab, the work presented in this study was not. Funding/Support: This work was supported in part by a start-up grant from the Dallas VA Research Corporation, a New Investigator Award from VISN 17 in the Department of Veterans Affairs, grant RG327A8/T from the National Multiple Sclerosis Society (NMSS), and a grant from the Viragh Foundation (O.S.). Support also came from grants NS37513 and NS44250 from the National Institutes of Health and grant RG2969-B-7 from the NMSS (M.K.R.). Additional support came from grants He2386/4-1 and He2386/4-2 of the Deutsche Forschungsgemeinschaft (B.H.) and grant N540993 from the National Institutes of Health (N.L.M.).

Additional Contributions: We thank our patients for participating in this study. Brittney Fort, Jane Lee, Janey Phillips, Jill Fowler, Nancy Perna, and Subir Sinha assisted in data acquisition.


Glucocerebrosidase Mutations and Risk of Parkinson Disease in Chinese Patients

G aucher disease (GD) is a recessive inherited glycolipid storage disorder caused by a deficiency of the lysosomal enzyme glucocerebrosidase (GBA). Recent observation of an association between Parkinson disease (PD) and GBA gene mutations in Ashkenazi Jewish patients has generated considerable scientific interest. However, data on this association in non–Ashkenazi Jewish populations is still limited. Two recent studies in white patients with PD reported a negative or questionable association with GBA mutations. The GBA L444P mutation appears to be the most common mutation among Chinese patients with GD in Taiwan. However, GD is extremely rare in our country. To our knowledge, there has not been a single reported case of GD in our population. Using a case-control methodology, we conducted a genetic screen of 2 common GBA mutations (L444P and N370S) in our ethnic Chinese patients with PD.

Methods. Our study included consecutive ethnic Chinese patients diagnosed with idiopathic PD by movement disorders neurologists at a tertiary referral center in Singapore. The PD diagnosis was made in accordance with the UK Parkinson’s Disease Society Brain Bank clinical criteria. Controls were healthy individuals of similar age, sex, and race without neurodegenerative diseases and were examined by us. The institutional ethics committee approved the study, and informed consent was obtained from all study subjects. We extracted DNA from lymphocytes according to a standardized protocol. Allelic discrimination using the 5′ nuclease activity assay was adapted to detect the L444P and N370S mutations. Primers and probes were designed using Primer Express 1.5 software (Applied Biosystems, Foster City, California). The amplification reactions were carried out in an ABI Prism 7700 Sequence Detection System (Applied Biosystems) with 2 initial steps (50°C for 2 minutes followed by 95°C for 10 minutes) and 40 cycles of a 2-step polymerase chain reaction (95°C for 15 seconds, 60°C for 1 minute). After the polymerase chain reaction, allelic-specific fluorescence was measured on the ABI Prism 7700 Sequence Detection System (Applied Biosystems) using Sequence Detection System 1.7 software for allelic discrimination. Sequence analysis was used to confirm the genotypes for all the positive samples (Figure). The numerical and categorical variables were compared using a Fischer exact test and t test. Statistical significance was defined as P<.05.
Results. A total of 678 subjects comprising 331 patients with PD and 347 controls similar in age and sex were analyzed. The mean±SD age was 70.0±11.0 years (range, 39-98 years) and 51.4% were men. The mean±SD ages at onset of patients with PD and controls was 64.0±10.0 years (range, 35-95 years) and 64.0±12.0 years (range, 29-90 years), comprising 48.7% men.

The frequency of the L444P and N370S mutations in patients with PD and controls was 8 of 331 vs 0 of 347 (2.4% vs 0.0%, \(P=0.003\)). All 8 patients with PD were heterozygous for the L444P mutation. However, the N370S mutation was not detected in all 778 subjects. Subset analysis revealed the association to be stronger in the group of subjects younger than 55 years (12.1% vs 0.0%, \(P=0.004\)) compared with those older than 55 years (1.3% vs 0.0%, \(P=0.06\)). The age at onset was lower in patients with PD with the L444P mutation compared with those without (49.0±13.0 years; range, 29-70 years; vs 64.0±11.0 years; range, 31-90 years; \(P=0.002\)), and more women were present in the former group (87.5% vs 47.7%, \(P=0.03\)).

Almost all patients with the L444P mutation presented with typical features of PD that were responsive to dopaminergic agents, and some developed levodopa-induced dyskinesias (Table). Previous mutational screening of the PARK1, PARK2, PARK6, PARK7, and PARK8 genes in these patients showed unremarkable findings.

Comment. We found a significantly higher prevalence of the L444P mutation in our patients with PD compared with controls, and the association was stronger in younger subjects and in women. The zero prevalence in the controls appeared compatible with the extreme rarity of GD in our population. Six of the 8 affected patients with PD did not have a family history of PD and the remaining 2 were siblings. The mean age at onset of these patients was significantly younger than the age of patients with PD without GBA mutations. One study in Ashkenazi Jewish patients reported a younger age at onset in PD with mutations, but this was not observed by others.2,6

A wide spectrum of neurological manifestations, such as epilepsy, cerebellar ataxia, psychiatric symptoms, dementia, and parkinsonism, has been reported in GD. GBA mutations have also been reported in other Lewy body disorders.7 The typical PD presentation and disease progression in all our 8 affected patients with PD was compatible with recent observations in Ashkenazi Jewish patients. The pathophysiologic link between PD and GD could be due to the impaired degradation of \(\alpha\)-synuclein aggregation as a result of lysosomal and proteasomal dysfunction.

Although the 2.4% frequency of the L444P GBA mutation in our patients with PD may appear low, this finding is significant due to the extreme rarity of GD in our population, supported by confirmation of the absence of this mutation among our healthy controls. While we cannot exclude the contribution of other rare GBA mutations, our study suggests that the L444P GBA mutation is associated with an increased risk of PD among the Chinese population.

Correspondence: Dr Tan, Department of Neurology, Singapore General Hospital, Outram Road, Singapore 169608 (gnrtek@sgh.com.sg).

Table. Clinical Features of Patients With Parkinson Disease (PD) With GBA Mutations

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Race</th>
<th>Age at Onset, y</th>
<th>Family History of PD</th>
<th>Typical Parkinsonian Features*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/44</td>
<td>Chinese</td>
<td>40</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2/F/46</td>
<td>Chinese</td>
<td>43</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3/M/51</td>
<td>Chinese</td>
<td>44</td>
<td>No</td>
<td>Yes with dyskinesias</td>
</tr>
<tr>
<td>4/F/70</td>
<td>Chinese</td>
<td>60</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5/F/35</td>
<td>Chinese</td>
<td>29</td>
<td>No</td>
<td>Did not start receiving levodopa</td>
</tr>
<tr>
<td>6/F/65</td>
<td>Chinese</td>
<td>58</td>
<td>No</td>
<td>Yes with dyskinesias</td>
</tr>
<tr>
<td>7/F/48</td>
<td>Chinese</td>
<td>45</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>8/F/77</td>
<td>Chinese</td>
<td>70</td>
<td>No</td>
<td>Yes with cognitive dysfunction</td>
</tr>
</tbody>
</table>

*Clinical features included rigidity, bradykinesia, and rest tremor and were responsive to treatment with levodopa.
and Zhao. Administrative, technical, and material support: Tan, Tong, Fook-Chong, Yih, Wong, Pavanni, and Zhao. Study supervision: Tan, Tong, Fook-Chong, Yih, Wong, Pavanni, and Zhao.

Financial Disclosure: None reported.

Funding/Support: This study was supported by the National Medical Research Council and SingHealth.

Additional Contributions: Lee Wei-Ling, MD, and Ivy Ng, MD, provided assistance and feedback.


Correspondence: Dr Gurrera, Psychiatry Service, VA Boston Healthcare System and Department of Psychiatry, Harvard Medical School, 940 Belmont St (116A), Brockton, MA 02301 (ronald.gurrera@va.gov).

In reply

We thank Dr Ronald Gurrera for his inspiring comments regarding our observation on cerebral salt-wasting syndrome (CSWS) in NMS.1 But we also would like to emphasize that extrapolations from a single case to the pathophysiology of a complex disorder should be taken with necessary care. Many questions have to be addressed in the future to give us a more comprehensive understanding of the pathophysiology of CSWS as well as NMS. For example, the definitive origin of BNP in CSWS has to be resolved in detail, whether it arises from peripheral nervous tissue (most likely adrenal medulla) or central or both. Are there other natriuretic peptides or natriuretic active molecules involved? What are the mechanisms in other pathological states, such as subarachnoid hemorrhage (SAH)? Does CSWS in SAH underlie also a dopamine deprivation and as a consequence a sympathoadrenal dysregulation as it suggests itself in NMS? If this should be the case, dopaminergic deprivation in patients with SAH could contribute to a poor outcome for such patients not only via salt-wasting but also via aggravation of cerebral vasospasms. The latter appears plausible because brain arteries are innervated intimately with sympathetic nerve terminals whose preganglionic neurons arise from the cervical spinal sympathetic cell columns. These neurons are surrounded by BNP-positive cell clusters, as Dr Gurrera pointed out in his correspondence, and are also innervated via hypothalamic dopaminergic projections.3 It remains unclear whether the known BNP expression pattern in intimate association with central sympathetic nervous system can be applied to humans because results are derived from animal studies. Recording levels of natriuretic peptides with aminergic neurotransmitter lev-

©2007 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Non-Human Traffic (NHT) User on 02/29/2020