Incidence of Parkinson disease among obligate carriers relatives of patients with Gaucher disease: a single-center report

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Paris, June 2012
Disclosure

None of the authors have financial or other considerations which may have impacted the results reported in this study.
History of the first clinical observations

- **1990: Israel**: Dr. Aghai asked about a possible association between Gaucher disease and Parkinson disease

- **1993: Italy**: Prof. Bembi introduces the “oldest patient with type 3 Gaucher disease” because she had Parkinson disease

- **1994: Jerusalem**: Presentation of a Gaucher patient with severe Parkinson disease, refractory to L-DOPA

- **1996**: First publication of 6 Gaucher patients with parkinsonism: common features = mild Gaucher and severe, early-onset Parkinson disease, refractory to L-DOPA

The glucocerebrosidase gene and Parkinson’s disease in Ashkenazi Jews
Orit Neudorfer, MD Thesis, 1994

- 150 DNA samples of patients with Parkinson disease from 5 Israeli centers
- Mutation analysis limited to N370S
- 94 (62%) males and 56 (38%) females
- No Parkinson patient had Gaucher disease or had a family history of Gaucher disease
- Mean age 71.3 years (range: 42-90)
- Mean age PD diagnosis: 65.6 years (range: 34-84) years
- PD characterized by Hoen & Yahr scale
16 (10.6%) patients with PD were carriers of N370S
One patient (0.6%) was homozygous
Carrier rate not statistically significant
Mean age PD onset in carriers: 57.0 (±11.1) years versus 66.8 (±9.7) years among non-carriers (p=0.003)
No statistically significant difference in Hoen &Yahr severity scale between carriers and non-carriers

Zimran, Neudorfer, Elstein. NEJM 2005;352:729 (letter)
Mutations in the Glucocerebrosidase Gene and Parkinson’s Disease in Ashkenazi Jews

Judith Aharon-Peretz, M.D., Hanna Rosenbaum, M.D., and Ruth Gershoni-Baruch, M.D.

- 99 Ashkenazi Jewish Israeli patients with idiopathic Parkinson disease
- Screened for six Gaucher mutations: N370S, L444P, 84GG, IVS+1, V394L, and R496H

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<table>
<thead>
<tr>
<th>Population</th>
<th>No. Tested</th>
<th>No. of Carriers (%)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Parkinson’s disease</td>
<td>99</td>
<td>31 (31.3)</td>
<td>22.2–40.4</td>
</tr>
<tr>
<td>Patients with Alzheimer’s disease</td>
<td>74</td>
<td>3 (4.1)</td>
<td>0.0–8.5</td>
</tr>
<tr>
<td>Controls</td>
<td>1543</td>
<td>95 (6.2)</td>
<td>5.0–7.4</td>
</tr>
</tbody>
</table>

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![Table 2. Rates of Carriage of Gaucher's Disease among Patients with Parkinson's Disease, Patients with Alzheimer's Disease, and Control Subjects.](image)

- 31.3% (31/99) patients with Parkinson disease had one or two mutant Gaucher mutations
- Patients with Parkinson disease had significantly greater odds of being carriers of Gaucher disease than patients with Alzheimer's disease or controls
- Among patients with Parkinson disease, those who were carriers of Gaucher disease were younger than those who were not carriers
Genotyping of Israeli Parkinson patients for 6 Gaucher disease mutations
Yaacov Applebaum, 2007 (unpublished)

- 96 Ashkenazi Jewish Israeli patients (of the original cohort of 150 DNA samples from Parkinson patients)
- 15 carriers: 12 N370S; 2 84GG; 1 R496H
- 1 patient identified: N370S/V394L

16.7% (16 / 96 patients) incidence of 6 Gaucher mutations among Parkinson patients versus incidence of 10.6% (16 / 150) when screening for only N370S
NIH Conference on Gaucher Disease and Parkinsonism. March 15 & 16, 2007
Odds Ratio for any Gaucher mutation in Parkinson patients versus Parkinson controls was 5.43 across all (16) centers.
Compared to Parkinson patients with no Gaucher mutation, those with a Gaucher mutation:

- presented earlier with Parkinson disease
- were more likely to have Parkinson-affected relatives
- were more likely to have atypical clinical manifestations
Clinical manifestations of Parkinson disease in patients with a Gaucher mutation and those with no mutation

3rd NIH Workshop on Gaucher Disease and Parkinsonism – April 2010
Incidence of Parkinson disease among obligate carrier relatives of patients with Gaucher disease: a single-center report

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*Department of Neurology, Columbia University Medical Center, NYC, NY, USA,

Paris, June 2012
Current Study

Aim: To present the incidence of Parkinson disease among obligate carrier relatives of patients with Gaucher disease based on personal interviews of patients from our large Jerusalem referral clinic for Gaucher disease.

Methods: All patients arriving at the Gaucher Clinic in Jerusalem during the period of mid-October 2011-mid June 2012 (8 months) were interviewed with regard to Parkinson disease in their families.
Incidence of Parkinson disease among obligate carriers of Gaucher disease: Results 1

- 153 GD patients (with 306 obligate carrier relatives) were interviewed
- 5.2% obligate carriers (16 / 306) with Parkinson disease
- Another 14 patients had non-obligate carrier relatives (grandparents, uncles, aunts) with Parkinson disease
Incidence of Parkinson disease among obligate carriers of Gaucher disease: Results 2

- Mean age onset Parkinson disease among obligate carrier relatives was **66.4 years** (range: 45-81 years)
- There was equal incidence of males (50%)
- Among obligate carrier relatives with Parkinson at least 60% obligate carrier relatives with Parkinson disease had the N370S mutation.
Incidence of Parkinson disease among patients with Gaucher disease whom I interviewed:

Results 3

- 8 PD+GD (with 16 obligate carriers) interviewed
- 6.3% (1/16) obligate carriers of PD+GD had Parkinson disease
- 5 males (62.5%)
- 5 N370S/N370S (62.5%); 3 N370S/other
- Mean age onset Parkinson disease: 58.9 years (range: 43-75 years)
Risk of Parkinson disease in type 1 Gaucher disease: a referral clinic’s experience

Eli Ben Chetrit, Roy N. Alcalay, Bettina Birmanns, Gheona Altarescu, Mici Phillips, Deborah Elstein, Ari Zimran

Gaucher Clinic¹ and the Department of Neurology³, Shaare Zedek Medical Center, Jerusalem, and the Hebrew University – Hadassah Medical School, Israel; Department of Neurology², Columbia University Medical Center, NYC, NY, USA

European Task Force on Brain and Neurodegenerative Lysosomal Storage Diseases

Frankfurt, March 2012
Incidence of Parkinson disease among SZMC patients with Gaucher disease

- 12 GD+PD patients
- 2.4% (12 / 510) adults at SZMC = GD+PD
- Mean age onset of Parkinson disease = 58.9 years (range: 43-75 years)
- 75% (9/12) are male
- 50% (6/12) of GD+PD are N370S / N370S
Comparison of SZMC obligate carriers + PD versus Gaucher patients + PD

- Mean age onset Parkinson is later in obligate carriers (66.4 versus 58.6 years)
- No male predominance in obligate carriers (50% versus 75%)
Incidence of Parkinson disease among obligate carriers of Gaucher disease: Conclusions

This is the first report of the incidence of Parkinson among obligate carriers of Gaucher disease that implicates:

- Later age of onset Parkinson among carriers than patients
- High prevalence of the N370S mutation
- Equal incidence of males and females with Parkinson among obligate carriers
Thank you for your attention!

We LOVE Paris!