Gaucher Disease and Parkinsonism: A Rare Disease Provides a Window into a Common Neurodegenerative Disorder

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"I live in a very small house, but my windows look out on a very large world.”  Confucius
Mendelian disorders provide a window into complex disease

Our knowledge about Gaucher disease can advance the field of Parkinson disease
Questions:

Isn’t Gaucher disease enough?

What more do we need to worry about?

GBA1- gene mutated in Gaucher disease

Glucocerebrosidase

Glucocerebroside + H₂O  \rightarrow  Ceramide + Glucose

(GCase)
Vast clinical variation is encountered in GD

- Hydrops fetalis
- Congenital ichthyosis
- Progressive neurologic degeneration
- Myoclonic epilepsy
- Parkinsonian manifestations
- Eye movement disorder
- Hydrocephalus, cardiac valve calcifications

Gaucher disease: a spectrum of phenotypes

- Non-neuronopathic
- Neuronopathic

GD1
- Asymptomatic
- Skeletal disease
- Visceral disease
- 2° neurologic involvement

GD3
- Neurologic manifestations
- Parkinsonian manifestations
- Hydrocephalus, cardiac valve calcifications
- Eye movement disorder
- Myoclonic epilepsy

GD2
- Rare disease
- Carrier rate=
- 1/100 general population
- 1/14 Ashkenazi Jews
Parkinson disease is common

- 2% of the population over 65 years
- 40,000 new cases/year
- 1 million people in the US

Contribution of both genetic and environmental factors
Parkinson disease (PD)

Includes: Bradykinesia (slowness of movement)
And at least one of the following:
- Muscular rigidity
- 4-6 Hz rest tremor
- Postural instability

Parkinsonism - term describing motor features of Parkinson disease

Dementia with Lewy bodies (DLB)
More severe cognitive deficits and more rapid disease progression

Disorders with parkinsonism- referred to as Lewy body disorders or synucleinopathies
Lewy bodies are inclusions containing aggregates of proteins in neurons.

Alpha-synuclein - a protein that aggregates and is found in Lewy bodies.

Lewy bodies are found in brain autopsy samples from patients with Parkinsonism.
The Parkinson story began in my clinic in 1996, with a single patient with GD who developed parkinsonism...

- Mild Gaucher disease - diagnosed at age 19
- Tremor at age 42; rigidity, masked facies, difficulty initiating movements and rapid deterioration of gait
- Progressive dementia - death at age 54

Was this a co-incidence?

- Other cases found in literature (Neudorfer *et al* 1996) and other clinics
- In 2003, we published a series of 17 similar patients (*Tayebi et al*, 2003) from around the world
The plot then thickens........

- Autopsy performed in Boston

- Contributed frozen brain samples:

   Serendipitous finding!

- Brain bank study: 12/57 had variants in GBA1

- None found among 44 control brains

*Study was very hard to get published!*
Family histories reveal parkinsonism in heterozygotes

- In a prospective study, **12** of **45** Gaucher probands had relatives with parkinsonism (*J Med Genet* 2004)
- Often, a parent or grandparent who was an obligate Gaucher carrier
- Similar findings from other Gaucher centers including Jerusalem

**Heterozygotes are at increased risk for parkinsonism**
International multi-center study of GBA1 mutations in PD

- 16 centers - 4 continents
  - >10,000 GBA1 genotypes from patients with PD and controls

- Subjects with PD are >5 times more likely to have a mutation in GBA1

- GBA1 carriers had earlier PD onset and more cognitive deficits

Second multi-center study in dementia with Lewy bodies (DLB) JAMA Neuro 2013

- 11 centers: 721 cases with DLB, 1962 controls
  - Odds ratio = 8.28

Gaucher mutations also play a role in DLB!
Finding a gene gives us a starting point

GBA1

Parkinson disease
Pathways to Parkinsonism

Many of the genes identified fall into lysosomal pathways.

Finding a gene can direct attention to a new pathway.
The number of publications on *GBA1* and Parkinsonism has rapidly grown!

Searching for *GBA1* you will find more papers about PD than GD!

Great interest by the pharma industry

“*GBA1*” and “Parkinson” PubMed search: results per year
NIH patient study: Can we find early clinical and imaging features predictive of parkinsonism in patients with \textit{GBA1} mutations?

**Clinical Studies**
- Physical exam
- Neurologic exam (UPDRS)
- Neurocognitive evaluation
- Olfactory testing
- Screens for non-motor symptoms

**Imaging Studies**
- MRI (structural abnormalities)
- PET Scans (L-Dopa metabolism)
- Trans-cranial sonogram (TCS) (ultrasound study)

Included:

- GD/PD
- GD carriers with PD
- GD with & FH of PD
- GD carriers & FH of PD

Dr. Grisel Lopez
Clinical study: Initial findings

Often, findings resemble ordinary PD

Our patients with PD

Some have DLB features (clinical and pathological)

Similar levodopa response

> 500 visits; >850 observations

Earlier age of PD onset (1.7-6 yr) Mean=49y

Positive family history more likely

Non-motor symptoms common- low UPSIT

Progression faster

More cognitive dysfunction

However, among our patients we have seen exceptions. Some of our patients have a slower progression and no cognitive problems
In our at-risk cohort of 93 individuals followed for up to 13 years, we have seen only one develop PD—clearly not the majority!
Focus on siblings

Ten sib pairs with GD

- Sibs seen 1-4 times over 1-12 years: complete battery of evaluations
- Thus far, no early indications of parkinsonism or changes in PET scans seen in non-PD sib \((\text{Mov Disorders, 2020})\)
- Many samples-plasma, serum, DNA, RNA, fibroblasts, RBCs, WBCs collected & stored

Being used to identify risk or protective alleles for PD
Remember…

Most Gaucher patients and carriers do **NOT** develop parkinsonism!

**GBA1 mutation** = **risk factor**

Challenge: To identify factors/genes increasing (or decreasing) risk for PD by

- Clinical evaluations
- Genomic approaches
New technologies are enabling us to unravel the factors contributing to our complex individual tapestries.

What is shared by GD patients with who develop PD?

Collaboration is essential when studying a rare disease.
Brain samples

• Exceptionally valuable and rare source of material for research investigations
• Collected at autopsy- takes planning and coordination
• Often stored by regional Brain Banks
• Comparing samples from individuals with Gaucher disease with & without Parkinson disease may help us to better understand what is going on
Can the Gaucher-Parkinson link lead to improved therapy?

Gaucher drugs (Enzyme Replacement & Substrate Reduction therapy) work, but are very expensive, inconvenient and do not cross the blood-brain-barrier.

Other strategies:
- Substrate reduction that crosses into the brain
- Gene therapy to the brain
- Strategies to get enzyme into the brain
- GCase chaperones

Disease-modifying therapy for Gaucher and Parkinson diseases: promote GCase folding to recover lysosomal function
GCase chaperones as therapy for GD
High-throughput screening approach
15 year collaboration with J. Marugan, W. Zheng, and C. Austin, NCATS

- Patient spleen- source of mutant GCase (N370S/N370S)
- HT Screen performed with 250K compounds
- New compounds identified: First non-inhibitory chaperones
- Lead compounds (758 and 607) identified

GD iPSC macrophages: compounds enhance enzyme activity, reverse lipid storage and restore macrophage function
iPSC-derived neurons are made from patient fibroblasts

Day 0                    5                        12

iPSC-derived neurons are made from patient fibroblasts.

EBs  Rosettes  NSCs  Dopaminergic neurons
N370S/N370S  N370S/N370S-PD

GD iPSC-dopaminergic neurons have decreased GCase and store the lipid.

The neurons mimic what is seen in patients.
Findings reversed with 607.
α-synuclein levels in iPSC dopaminergic neurons from patients with Gaucher disease and PD

Elevated levels of α-synuclein seen

α-synuclein levels are reduced when cells were treated with our lead GCase chaperone 607

Suggests that drugs that increase GCase may work to treat Parkinson disease: Lots of work ahead!
Take-home messages:

• Mutation in the Gaucher gene, $GBA1$ is a risk factor for Parkinson disease, even in carriers.
• However, most patients and carriers will never develop Parkinson disease.
• Learning more about this connection will improve our understanding of both disorders.
• New drug development for Parkinson disease may be beneficial for Gaucher disease.
How to contribute to this research:

• Get involved in a study- NIH, Michael J Fox Foundation, other research centers
• Both patients with GD and carriers (with or without Parkinson disease) can be valuable
• Consider sample and tissue donations
• Keep up to date on new therapies: clinicaltrials.gov
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