PRACTICE AID

Cracking the Code: The Link Between Gaucher Disease and GBA-Associated Parkinson's Disease[1-17]

Full abbreviations, accreditation, and disclosure information available at **PeerView.com/GWQ40**

PeerView Neurology

GCA GAUCHER COMMUNITY ALLIANCE

The Gaucher Disease and GBA-Associated Parkinson's Disease Connection

Lysosomal diseases (LDs)
comprise 70+ rare, inherited disorders; Gaucher disease (GD) is the most common LD

Some GD cases are first identified following a PD diagnosis,
underscoring the diagnostic overlap

Neurological symptoms related to PD may precede GD diagnosis

Clinicians managing PD should be alert
early referrals and genetic screening are essential for *GBA1*-PD

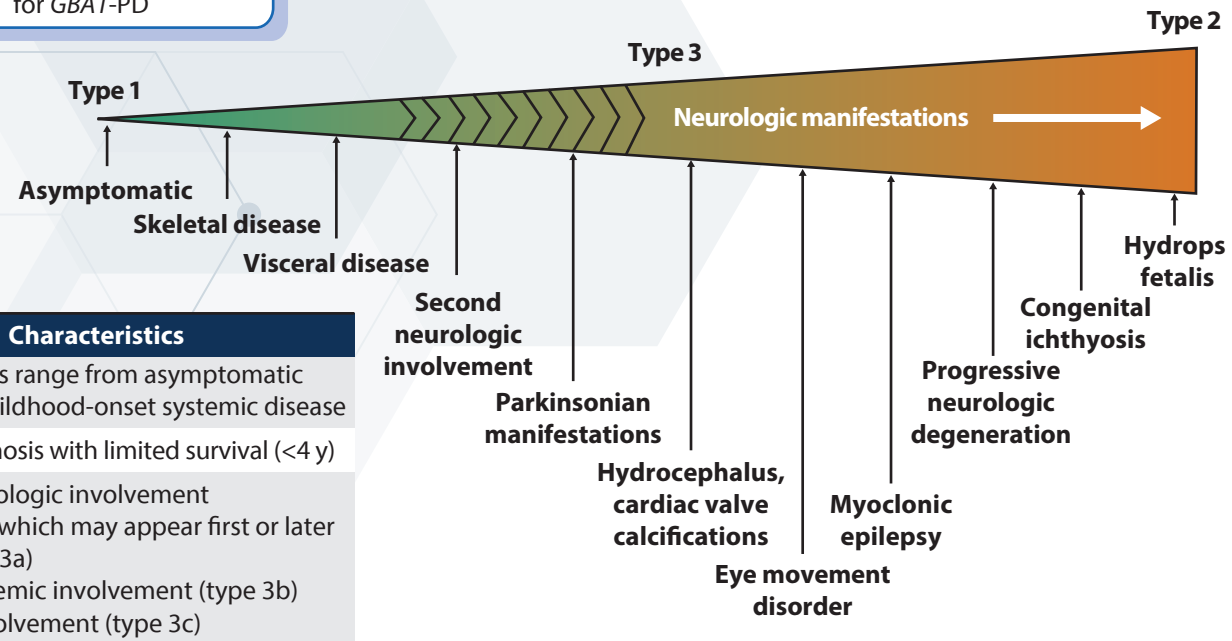
GBA-associated Parkinson's disease (GBA-PD)
is now recognized as distinct from idiopathic PD, with unique genetic and clinical features

Gaucher Disease
A rare, inherited multisystem disorder

Characterized by
- Accumulation of Gaucher cells (activated macrophages) in multiple organs, such as the liver, spleen, bone marrow, and lungs
- Has clinically recognizable types based on primary involvement of CNS and rate of disease progression
- **Progressive neurodegeneration in neuronopathic types: type 2 or acute and type 3 or chronic neuropathic Gaucher disease**

Incidence of Gaucher Disease
- Global incidence across all types: 0.45-25.0 per 100,000 people
- In the United States: approximately 1 in 50,000 to 100,000
- Among Ashkenazi Jewish individuals: approximately 1 in 500 to 1,000

Neurologic Manifestations by GD Type



GD Type	Prevalence, %	Characteristics
Type 1, non-neuronopathic	>95	Symptoms range from asymptomatic patients to childhood-onset systemic disease
Type 2, acute neuronopathic	~1	Severe prognosis with limited survival (<4 y)
Type 3, subacute neuronopathic	~5	Variable neurologic involvement • Myoclonus which may appear first or later in life (type 3a) • Severe systemic involvement (type 3b) • Cardiac involvement (type 3c)

PRACTICE AID

Cracking the Code: The Link Between Gaucher Disease and GBA-Associated Parkinson's Disease[1-17]

Full abbreviations, accreditation, and disclosure information available at **PeerView.com/GWQ40**

PeerView Neurology

GCA GAUCHER COMMUNITY ALLIANCE

GBA-Associated Parkinson's Disease

Features	
Onset	Earlier in homozygotes > heterozygotes > noncarriers
Progression	Faster than typical PD
Motor symptoms	Less bradykinesia, rigidity, and rest tremor
Disease complications	More dyskinesia, motor fluctuations
Nonmotor symptoms	Early cognitive impairment
Medication response	+
Medication response	±, concern for post-op cognitive decline

- Incidence of GBA-PD: 3%-20% among PD cohorts; 1%-5% among healthy cohorts; varies with ethnic population

- Heterozygous *GBA1* mutations occur in ~5%-10% of PD patients overall (up to ~20% in Ashkenazi Jewish PD patients), making *GBA1* the single most common genetic risk factor for PD

- Most carriers will NOT develop PD in their lifetime (reduced penetrance)
  - *GBA1* variants confer increased risk of PD but with reduced penetrance
  - Estimated penetrance is only ~1%-14% by 60 years of age, rising to ~10%-30% by 80 years of age

PRACTICE AID

Cracking the Code: The Link Between Gaucher Disease and GBA-Associated Parkinson's Disease[1-17]

Full abbreviations, accreditation, and disclosure information available at **PeerView.com/GWQ40**

PeerView Neurology

GCA GAUCHER COMMUNITY ALLIANCE

Common GBA Variants and PD Risk

GBA1 Variant (protein change)	GD Classification	PD Risk (OR)	Notes
N370S (Asn370Ser) (aka *N409S*)	Mild (GD1)	~2-8	• Most common GD mutation • Increases PD risk but later onset vs severe variants
L444P (Leu444Pro) (aka *L483P*)	Severe (GD2/3)	~6-30	• Common severe mutation • High PD risk; earlier onset and higher dementia risk
E326K (Glu326Lys)	Risk only (non-GD)	~1.6-3.3	• Does not cause GD on its own • Fairly common allele (~1% frequency) associated with PD and cognitive decline
T369M (Thr369Met) (aka *T408M*)	Risk only (non-GD)	~1.4-5.0	• Does not cause GD • Increases PD risk • Linked to earlier PD onset and faster progression
*84dupG (84insGG, Leu29Alafs*18)*	Severe (frameshift)	~10-14	• Frameshift GD mutation (historical "84GG" allele); confers high PD risk
R496H (Arg496His) (aka *R535H*)	Mild (GD1)	~3-4	• Mild GD variant seen in PD • Intermediate risk increase

Comparative Clinical Characteristics by *GBA1* Mutation Status

Clinical Feature	Severe *GBA* Mutation (*L444P*)	Mild *GBA* Mutation (*N370S*)	No *GBA* Mutation (Idiopathic PD)
Typical PD onset age	Earlier (often ~5 years younger than idiopathic)	Slightly earlier than idiopathic but later than severe carriers	Later onset (older adulthood); baseline risk group
Motor symptom progression	Faster decline in motor function and earlier complications (eg, fluctuations)	Intermediate progression; noticeable but not as accelerated as severe carriers	More gradual progression (slower decline relative to GBA-PD)
Cognitive impairment	High risk; earlier and more severe cognitive decline; frequent PD dementia	Moderate risk; cognitive issues can occur (eg, mild cognitive impairment), but dementia tends to occur later than in severe GBA-PD	Lower risk; many patients have no dementia until very late disease (if at all)
Nonmotor symptoms	Pronounced (depression, REM sleep disorder, autonomic dysfunction are common)	Present, with higher frequency than idiopathic PD, but variable in severity	Present in some, but generally less frequent or severe than in *GBA* carriers
Disease duration	Often shorter because of rapid progression and earlier dementia	Potentially long, but quality of life may be affected by mid-stage cognitive/mood symptoms	Often long (20+ years), especially if cognition is preserved

1. Linari S et al. *Clin Cases Miner Bone Metab*. 2015;12:157. 2. Huang WJ et al. *Eur Rev Med Pharmacol Sci*. 2015;19:1219. 3. Mehta A. *Eur J Internal Med*. 2006;17:S2. 4. Baris HN et al. *Pediatr Endocrinol Rev*. 2014;12:72. 5. https://ghr.nlm.nih.gov/condition/gaucher-disease. 6. Machaczka M et al. *J Inher Dis*. 2011:34: 233-235. 7. Castillon GC et al. *J Clin Med*. 2022;12:85. 8. Cook L et al. *Neurol Clin Pract*. 2021;11:69-77. 9. Cook L et al. *Curr Neurol Neurosci Rep*. 2021;21:17. 10. Goker-Alpan O et al. *J Med Genet*. 2004;41:937-940. 11. Sidransky E et al. *N Engl J Med*. 2009;361:1651-1662. 12. Klein C et al. *Cold Spring Harb Perspect Med*. 2012;2:a008888 2. 13. Smith L et al. *Cells*. 2022;11:1261. 14. Horowitz M et al. *Hum Mutat*. 1998;12:240-244. 15. Smith L et al. *Cells*. 2022;11:1261. 16. Cohen ME et al. *Parkinsonism Relat Disord*. 2024;124:106990. 17. Sidransky E. *Mol Genet Metab*. 2004;83:6-15.