Neuroimaging in Glucocerebrosidase-Associated Parkinsonism: A Systematic Review

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ABSTRACT: Background: Mutations in the GBA gene cause Gaucher’s disease (GD) and constitute the most frequent genetic risk factor for idiopathic Parkinson’s disease (iPD). Nonmanifesting carriers of GBA mutations/variants (GBA-NMC) constitute a potential PD preclinical population, whereas PD patients carrying some GBA mutations/variants (GBA-PD) have a higher risk of a more aggressive disease course. Different neuroimaging techniques are emerging as potential biomarkers in PD and have been used to study GBA-associated parkinsonism.

Objective: The aim is to critically review studies applying neuroimaging to GBA-associated parkinsonism.

Methods: Literature search was performed using PubMed and EMBASE databases (last search February 7, 2022). Studies reporting neuroimaging findings in GBA-PD, GD with and without parkinsonism, and GBA-NMC were included.

Results: Thirty-five studies were included. In longitudinal studies, GBA-PD patients show a more aggressive disease than iPD at both structural magnetic resonance imaging and 123-fluoropropylcarbomethoxyiodophenyltropane single-photon emission computed tomography. Fluorodeoxyglucose-positron emission tomography and brain perfusion studies reported a greater cortical involvement in GBA-PD compared to iPD. Overall, contrasting evidence is available regarding GBA-NMC for imaging and clinical findings, although subtle differences have been reported compared with healthy controls with no mutations.

Conclusions: Although results must be interpreted with caution due to limitations of the studies, in line with previous clinical observations, GBA-PD showed a more aggressive disease progression in neuroimaging longitudinal studies compared to iPD. Cognitive impairment, a “clinical signature” of GBA-PD, seems to find its neuroimaging correlate in the greater cortical burden displayed by these patients as compared to iPD. © 2022 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: 123-fluoropropylcarbomethoxyiodophenyltropane-SPECT; glucocerebrosidase; magnetic resonance imaging; multiomics; Parkinson’s disease; parkinsonism; positron emission tomography; prodromal stage; single-photon emission computed tomography; transcranial sonography

Parkinson’s disease (PD) is a complex neurodegenerative disorder characterized by multiple motor and nonmotor symptoms.1 In the past decades, more than 20 genes have been related to parkinsonism.2 Following the observation of higher risk of developing parkinsonism in patients affected by Gaucher’s disease (GD), a lysosomal disorder...
caused by mutations in the GBA gene (which encodes for lysosomal glucocerebrosidase -GCase-), GBA mutations have been found to constitute the greatest risk factor for sporadic PD, although with variations in mutation frequency based on the characteristics of the observed population.\(^3\) The molecular mechanisms that lead to increased PD risk in GBA mutation carriers are multiple and not fully elucidated yet; they include α-synuclein aggregation, lysosomal-autophagy dysfunction, and endoplasmic reticulum stress.\(^4\) GBA mutations can be distinguished based on the classification in use for GD: mild mutations are those that cause GD type I (nonneurenopatic), severe mutations are those that cause GD types II and III (neuronpathic)—however, some mutations that are linked to PD are nonpathogenetic in GD.\(^5\) Moreover, dysfunction of GCase has been demonstrated in PD without GBA mutations, suggesting its interaction with other pathogenetic mechanisms.\(^6,7\)

PD with GBA mutations/variants (GBA-PD) does not present pathognomonic features that distinguish it from “idiopathic” PD (iPD). However, depending on the mutation, GBA-PD is associated to an earlier onset; more aggressive disease course and reduced survival; and an increased risk of dementia, motor disability, dysphagia, and autonomic dysfunction.\(^8,9\)

Nonmanifesting carriers of GBA mutations/variants (GBA-NMC) and GD patients without parkinsonism constitute a potential preclinical population to study the pathophysiology of the disease and to target in case of development of neuroprotective therapies. In particular, drugs that target GCase pathways are currently under investigation in clinical trials as neuroprotective therapies in PD.\(^10\)

Considering the potential relevance of GBA mutations/variants for prognostic and therapeutic applications, the search for GBA-related biomarkers is becoming essential.

In clinical practice, conventional imaging techniques are used to support the diagnosis of PD and to investigate specific clinical features.\(^1\) Other techniques, such as advanced structural magnetic resonance imaging (MRI) or functional MRI (fMRI), are used in research settings (for review, see references 11-13). The focus is on the potential role of neuroimaging as biomarkers for diagnosis, to assess disease progression and monitor therapeutic interventions and to understand the pathophysiology of the disease.\(^14\) In the past years, several studies applied imaging techniques in GBA-PD, GD patients with (GD-p) and without parkinsonism, and GBA-NMC to elucidate aspects of pathogenesis in GBA-PD and to identify at-risk populations.

The aim of the present systematic review is to critically summarize evidence from these studies, to update a previous review on the topic,\(^15\) and to analyze and discuss the emerging controversies in the field, trying to address apparent discrepancies.

## Patients and Methods

### Search Strategy

Literature search was performed using PubMed and EMBASE (last search: February 7, 2022). Methods and search string are provided in Supplementary Material. The PRISMA flowchart is shown in Supplementary Figure S1. The details of the studies (number of participants, methods, etc.) are presented in Supplementary Table S1 and Tables 1-5. As the definition of “iPD” and “controls” differs across studies, we invite the reader to search for details in Supplementary Table S1.

### Results

#### Structural MRI

Six studies were included (Supplementary Table S1 and Table 1).

PD is not associated with alterations in conventional structural imaging scans.\(^1\) However, advanced MRI techniques allow the quantification of iron accumulation in the substantia nigra (SN) using neuromelaninsensitive MRI, structural gray matter (GM) changes (eg, GM volume or cortical thickness), and microstructural white matter (WM) integrity. Diffusion tensor imaging (DTI), in particular, allows the assessment of microstructural tissue integrity; the most commonly used DTI indices include fractional anisotropy (FA)—a measure of the directionality of water diffusion—and mean diffusivity—a measure of the absolute magnitude of diffusion (for review, see references 13 and 14).

In GBA-NMC, no structural GM differences have been reported compared to controls\(^16,18\) or to nonmanifesting carriers of LRKK2 mutations (LRKK2-NMC).\(^19\)

In GD patients (including 2 GD-p patients) a negative correlation between SN echogenicity—a sonographic feature considered to reflect iron accumulation (see later)—and iron-sensitive MRI-T2 hypointensity of SN pars compacta has been reported: the authors suggested that this finding might be related to disturbance in iron metabolism involving deep brain structures in GD.\(^21\)

In a study, GBA-PD patients showed a left-sided prevalent pattern of cortical thinning involving mainly temporal, parietal, and occipital regions compared to iPD and controls.\(^18\) Longitudinal follow-up of this cohort showed a greater cortical thinning of posterior regions and additional greater involvement of frontal and orbitofrontal lobes in GBA-PD compared to iPD, whereas the pattern of subcortical GM atrophy was similar in the two PD groups. After 5 years, iPD patients reached a similar pattern of cortical thinning to GBA-PD at baseline. These imaging findings were in line with clinical observations demonstrating a more rapid trajectory of motor and cognitive impairment in GBA-PD compared to iPD.\(^18\) Also a study conducted
| Studies | MRI method | Sample | Clinical features | Cognition | Clinical findings | Imaging findings | Conclusions |
|---------|------------|--------|------------------|-----------|------------------|-----------------|-------------|
| Segev et al<sup>16</sup> | Whole-brain analysis | 18 GBA-NMC, 17 CTRL | Age GBA-NMC = 43.7 ± 7.8, CTRL = 44 ± 9.2 | MMSE GBA-NMC = 28.8 ± 1.2, CTRL = 29.6 ± 0.7 | GBA-NMC = no differences (vs. CTRL) | No differences in GM (vs. CTRL) | No GBA-specific patterns |
| Caminiti et al<sup>17</sup> | ROI-based analysis | 46 GBA-PD, 339 iPD (281 LO-iPD, 58 EO-iPD), 59 CTRL | Age GBA-PD = 59.9 ± 9.6, EO-iPD = 47 ± 4.8, LO-iPD = 64.8 ± 7.1, CTRL = 59.2 ± 10.7 | MoCA GBA-PD = 26.9 ± 2.5, EO-iPD = 28 ± 2.3, LO-iPD = 27 ± 2.3, CTRL = IC > 26 | GBA-PD = † GM volume of whole left putamen, whole right putamen, left anterior putamen, right posterior putamen, left ventral striatum, right ventral striatum, right thalamus, left hippocampus, right hippocampus, left amygdala, right amygdala (vs. EO-iPD) and left posterior putamen, right caudate nucleus, right thalamus (vs. LO-iPD) | GBA-PD = more aggressive disease (vs. EO-iPD) | GBA-PD = more aggressive disease (vs. EO-iPD) |
| Leocadio et al<sup>18</sup> | Whole-brain/ROI-based analysis | 10 GBA-PD, 20 iPD, 22 CTRL | Baseline | MMSE GBA-PD = 28 ± 1.7, iPD = 28.9 ± 1.2, CTRL = 29.8 ± 0.5 | GBA-PD = no differences (vs. iPD); † MMSE (vs. CTRL) | GBA-PD = † cortical thinning of left temporal, parietal, and occipital gyri (vs. CTRL and iPD) | GBA-PD = † cortical thinning of left temporal, parietal, and occipital gyri (vs. CTRL and iPD) |
| Thaler et al<sup>19</sup> | ROI-based analysis | 12 GBA-PD, 9 LRRK2-PD, 57 iPD, 14 GBA-NMC, 41 LRRK2-NMC, 49 CTRL | Age GBA-PD = 65.5 ± 11.4, LRRK2-PD = 60.4 ± 12.5, iPD = 653 ± 9, GBA-NMC = 49.3 ± 9, LRRK2-NMC = 49 ± 10.9, CTRL = 47.5 ± 11.5 | MoCA GBA-PD = 24.8 ± 4.6, LRRK2-PD = 26.6 ± 2.9, iPD = 25.3 ± 2.6, GBA-NMC = 26.8 ± 2.3, LRRK2-NMC = 26.3 ± 2.8, CTRL = 26.7 ± 2.2 | GBA-PD = no difference (vs. iPD); † GBA-PD and iPD = † disease duration, motor symptoms, depression, † hyposmia (vs. LRRK2-PD) | PD (all) = † subcortical volumes and cortical thinning (vs. CTRL); no difference related to genetics | No GBA-specific patterns |
| Agosta et al<sup>20</sup> | Whole-brain/ROI-based analysis | 15 GBA-PD, 14 iPD, 16 CTRL | Age GBA-PD = 64 ± 8, iPD = 64 ± 7, CTRL = 64 ± 8 | MMSE GBA-PD = 28 ± 3, iPD = 27 ± 2 | GBA-PD had dementia (MDS criteria) vs. 0 in other groups | No other differences between GBA-PD and iPD | GBA-PD = † FA olfactory tracts, corpus callosum, and anterior limb of the internal capsule bilaterality, right anterior external capsule, and left cingulum, parahippocampal tract, partial portion of the superior longitudinal fasciculus, and occipital white matter (vs. CTRL); external capsule bilaterality and left SLF (vs. iPD); body and genu of the corpus callosum, olfactory tract, anterior limb of the internal capsule, cingulum bilaterality (vs. iPD and CTRL) | GBA-PD = widespread WM alterations (vs. iPD) |

(Continues)
### TABLE 1

| Studies | MRI method | Sample | Clinical features | Cognition | Clinical findings | Imaging findings | Conclusions |
|---------|------------|--------|-------------------|-----------|-------------------|-----------------|-------------|
| Böttcher et al. | ROI-based analysis | 2 GD-p, 6 GD | Age GD-p = 49, 62, GD = 23-66 | IC = MMSE ≥ 25 | Whole group | GD and GD-p = positive correlation between SN and T2-hypointensity of SN and parietal cortex | GD = possible iron metabolism alterations in SN |
| | | | UHDRS III GD-p = 15.5, GD = 0-1 | | | | |
| Filippi et al. | | | | | | | |
| **MRIs spectroscopy (MRSI)** | | | | | | | |
| Brockmann et al. | Combined proton (1H) and phosphorous (31P) MRSI | 13 GBA-PD, 19 CTRL | Age GBA-PD = 56, 30-69, CTRL = 54 (40-71) | NA | NA | GBA-PD = ND | GBA-PD = altered membrane phospholipid metabolism vs. CTRL |
| | | | UHDRS III GBA-PD = 32 (17-43) | | | | |
| | | | HY GBA-PD = 2.5 (2-4.5) | | | | |
| | | | | | | | |
| Functional MRI (fMRI) | | | | | | | |
| Sengin et al. | Resting-state fMRI (1H and 31P) MRSI | 18 GBA-NMC, 17 CTRL | Age GBA-NMC = 45.7 ± 7.8, CTRL = 44 ± 9.2 | MMSE GBA-NMC = 28.8 ± 1.2, CTRL = 29.6 ± 0.7 | GBA-PD = no difference (vs. CTRL) | GBA-NMC = FC between left posterior putamen and left pontine tegmentum and pontine tegmentum (vs. CTRL) | GBA-NMC = alterations in striato-cortical FC and early impairment of somatosensory system (vs. CTRL) |
| | | | UHDRS III GBA-NMC = 25.3 ± 9.8, CTRL = 23.7 ± 9.1 | | | | |
| | | | HY GBA-PD = 2.3 (2-3.3), HY CTRL = 2.5 (1.1) | | | | |
| Greuel et al. | Resting-state fMRI (OFF condition) | 13 GBA-PD, 42 iPD | Age GBA-PD = 66.7 ± 8.6, iPD = 65.0 ± 10.2 | Dementia was excluded (MDS criteria) | GBA-PD = FC between left caudate nucleus and the occipital cortex and between the right nucleus accumbens and the left superior parietal and right fusiform cortex (vs. iPD) | GBA-PD = FC between caudate nucleus and the occipital cortex and between the right nucleus accumbens and the left superior parietal and right fusiform cortex (vs. iPD) | GBA-PD = more severe alterations vs. iPD, even in brains without dementia |
| | | | UHDRS III GBA-PD = 23.7 ± 9.1, iPD = 23.7 ± 2.3, CTRL = 23.7 ± 9.1 | | | | |
| | | | HY GBA-PD = 2.5 (2-3.3), HY CTRL = 2.5 (1.1) | | | | |
| Bergman et al. | Task fMRI = Stroop interference task and N-back working memory task | 10 GBA-NMC, 21 LRRK2-NMC, 22 CTRL | Age GBA-NMC = 30.4 ± 2.39, LRRK2-NMC = 47.9 ± 5.19 | IC = MoCA > 23 | GBA-PD = no differences (vs. LRRK2-NMC and CTRL) | GBA-NMC = FC activity in cognitive tasks in the bilateral medial frontal and precentral gyrus and the lingual gyrus (vs. LRRK2-NMC and CTRL) | GBA-NMC = FC activity in cognitive tasks in the bilateral medial frontal and precentral gyrus and the lingual gyrus (vs. LRRK2-NMC and CTRL) |
| | | | UHDRS III GBA-NMC = 25.3 ± 9.8, LRRK2-NMC = 23.7 ± 9.1 | | | | |
| | | | | | | | |

*Studies are ordered chronologically. If not specified, the studies are cross-sectional. Information on how controls and iPD were selected is provided in Supplementary Table S1. See Supplementary Table S1 for details of classification of GBA mutations/variants. When available, mean ± standard deviation is reported; otherwise, mean, range (separated by –), single values (separated by comma), or IC is reported. If no information is available, NA is reported. If details for the subgroup that underwent imaging study are not available, results for the whole group are reported.

1Subjects from the Parkinson’s Progression Markers Initiative (PPMI) cohort.

2Longitudinal study. The study is divided into two rows for clarity in the table: the second row refers to the longitudinal analysis, 5-year follow-up.

3Compared to iPD, GBA-PD showed a greater disease severity progression (HY and UPDRS total and subscores II and III). Compared to iPD, GBA-PD worsened over time in terms of attentional and visuospatial skills and in their ability to inhibit cognitive interference. Group x time interactions also showed that GBA-PD patients progressed in visuospatial deficits more than iPD.

4Antiparkinsonian medication was discontinued for a minimum of 12 hours (levodopa) and up to 3 days (dopamine agonists).

5A cognitive test battery covered the following domains: executive function, memory, attention, language, and visuospatial abilities, from which a global cognition z score was computed using age- and education-adjusted standard norms. The global cognition z score was significantly lower when the HDB-II score was included as a covariate.

6Abbreviations: MRI, magnetic resonance imaging; GBA-NMC, nonmanifesting carriers of GBA mutations/variants; CTRL, controls; UHDRS III, Unified Parkinson’s Disease Rating Scale, Part III; MMSE, Mini-Mental State Exam; GM, gray matter; ROI, region of interest; iPD, idiopathic Parkinson’s disease; LO-iPD, late-onset idiopathic Parkinson’s disease; EO-iPD, early-onset idiopathic Parkinson’s disease; GBA-PD, Parkinson’s disease with GBA mutations/variants; HY, Hoehn and Yahr score; MoCA, Montreal Cognitive Assessment; SCOPA-AUT, Scale for Outcomes in Parkinson’s disease-Autonomic; RBDSQ, REM Sleep Behavior Disorder Screening Questionnaire; LRRK2-PD, Parkinson disease with LRRK2 mutations; LRRK2-NMC, nonmanifesting carriers of LRRK2 mutations/variants; FA, fractional anisotropy; SLF, superior longitudinal fasciculus; WM, white matter; GD-p, GBA with parkinism; GD, Gaucher’s disease; IC, inclusion criteria; NMS, nonmotor symptoms; SN, substantia nigra; MRSI, magnetic resonance spectroscopic imaging; NA, not available; NAA, N-acetylaspartate; tCho, total choline; GPE, glycerophosphocholine; ATP, adenosine triphosphate; ADP, adenosine diphosphate; Pi, inorganic phosphate; PCr, phosphocreatine; MDS, Movement Disorder Society; BDII, Beck’s Depression Inventory; II, FC, functional connectivity.
on the Parkinson’s Progression Markers Initiative (PPMI) cohort reported significant GM differences in GBA-PD compared with iPd patients. In particular, both GBA-PD and late-onset (LO)-iPD showed greater structural volume reductions compared with the early-onset (EO)-iPD group. The clinical follow-up (up to 6 years) in this cohort showed greater worsening in motor, cognitive, and autonomic functions in GBA-PD versus EO-iPD and in LO-iPD versus EO-iPD but no differences between GBA-iPD and LO-iPD. LO-iPD is associated with a more aggressive form of disease; the findings of this study (see the Nigrostriatal Imaging section) support the hypothesis that GBA mutations participate to accelerate the neurodegenerative processes in PD.

Conversely, in other studies, no differences in GM have been reported between GBA-PD, iPd, and controls and between GBA-PD, PD with LRRK2 mutations (LRRK2-PD), and iPd, although, in the latter study, lower GM volumes were reported in bilateral hippocampus, nucleus accumbens, caudate, thalamus, putamen and amygdala, and the right pallidum in patients with PD (eg, GBA-PD, LRRK2-PD, and iPd) compared to unaffected participants (eg, GBA-NMC, LRRK2-NMC, and controls).

Differences in microstructural WM integrity that may have an impact on the clinical manifestations of the disease, including cognitive impairment, have been reported in GBA-PD. Compared with controls, GBA-PD showed decreased FA bilaterally in the olfactory tracts; genu and body of the corpus callosum; and anterior limb of the internal capsule in the right anterior external capsule, left cingulum bundle, left parahippocampal tract, left parietal portion of the superior longitudinal fasciculus (SLF), and left occipital WM. Compared to iPd, GBA-PD showed decreased FA in the external capsule bilaterally and left SLF. Compared with both controls and iPd, GBA-PD showed decreased FA in the body and genu of the corpus callosum, olfactory tract, anterior limb of the internal capsule, and cingulum bilaterally. In all PD patients, FA values of the body and genu of the corpus callosum, external capsule, and olfactory tracts correlated with verbal fluency. No differences in WM were reported between iPd and controls.

### MR Spectroscopy

One study was included (Supplementary Table S1 and Table 1).

Proton MR spectroscopy of the brain is a noninvasive, in vivo technique that allows investigation into regional chemical environments. Only one study applied MR spectroscopy to the study of GBA-PD. Compared with controls, mesostriatal membrane metabolites (eg, N-acetylaspartate [NAA]), but not energy status (high-energy phosphates and low-energy metabolites), were altered in GBA-PD, suggesting that a primary membrane dysfunction, rather than energetic metabolism dysfunction, may underlie the pathogenesis of GBA-PD. It must be considered, however, that lowered NAA has also been detected in the SN and other regions in iPd compared to controls; indeed, in the absence of iPd controls, it is not possible to determine whether these findings are related to the neurodegenerative mechanism underlying PD, in general, or to GBA mutations/variants, in particular.

### Functional MRI

Three studies were included (Supplementary Table S1 and Table 1).

Two fMRI approaches exist to study brain neuronal activity: resting-state fMRI and task-based fMRI. The first method measures the intrinsic fluctuations of the BOLD signal between different brain regions during rest to assess functional connectivity alterations within and between resting-state functional networks. Task-based fMRI includes the performance of a task during the fMRI acquisition, eliciting the activation of task-specific areas (eg, motor, sensitive, and visual). This approach is useful to assess specific patterns of brain activity changes in different conditions or after specific trainings.

A study showed increased resting-state functional connectivity between left posterior putamen and left postcentral gyrus and between left caudate and right parietal operculum and planum temporale in GBA-NMC compared to controls. The authors suggest that an early impairment of the striato-somatosensory network might precede the involvement of the motor system and, thus, the appearance of symptoms in GBA carriers. Another study focused on GBA-NMC and controls, including LRRK2-NMC. Differently from the previous study, the aim was the evaluation of cognitive task performance in the presymptomatic stage of PD. The authors characterized the cognitive profile and functional activation patterns of GBA-NMC in depth while performing two separate fMRI cognitive tasks (Stroop interference task and N-back working memory task). Similar cognitive and task-related performance combined with a higher functional activity in the right medial frontal gyrus and reduced task-related activity in the left lingual gyrus during the Stroop task was found in GBA-NMC relative to LRRK2-NMC and controls. On the N-back task, no whole-brain differences were found between groups. The authors suggest that GBA-NMC present differential cerebral compensatory mechanism that might allow adequate cognitive performance in the preclinical stages of PD.

Only one study explored the resting-state fMRI features in GBA-PD patients in OFF condition. Although
### TABLE 2  Positron emission tomography studies

| Studies | Sample | Clinical features | Cognition | Clinical findings | Imaging findings | Conclusions |
|---------|--------|------------------|-----------|------------------|-----------------|-------------|
| Greuel et al. | 12 GBA-PD, 34 iPD | Whole group | Dementia was excluded (MDS criteria) | GBA-PD = [global cognition z score; 
\[ \text{BDI-II (vs. iPD)} \] | GBA-PD = [PDPR expression; trend for higher expression of PDP < PDCP; \( \text{metabolism in medial and lateral parietal cortex (vs. iPD)} \] | GBA-PD = more severe alterations vs. iPD, even in carriers without dementia |
| Schindlbeck et al. | 12 GBA-PD (including 1 GD), 14 LRRK2-PD, 14 iPD, 14 CTRL | Age 64–69, UPDRS III/HY NA | Only akinetic-rigid PD | No differences between groups | GBA-PD = [PDPR (vs. LRRK2-PD and iPD); PDPR comparable to iPD; SMA hypometabolism may be related to clinical characteristics (akinesia) of GBA-PD] | GBA-PD = more aggressive disease vs. iPD and LRRK2-PD |
| Barret et al. | 3 GBA-PD | Age 64–69, UPDRS III/HY NA | UPDRS III mentation score = 0–2 | NA | GBA-PD = [PDPR (vs. LRRK2-PD and iPD); SMA hypometabolism may be related to clinical characteristics (akinesia) of GBA-PD] | GBA-PD = findings consistent with iPD |
| Kono et al. | 3 GBA-PD (including 1 GD), 3 GBA-NMC | Age 44–76, GBA-NMC = 47–74 | MMSE, GBA-PD = 24–30, GBA-NMC = 24–30 | All [global cognition; \( \text{metabolism in the frontal cortex, including the SMA; GBA-PD = [global cognition; \( \text{metabolism in parieto-occipital cortex]}} \] | GBA-PD = [PDPR (vs. LRRK2-PD and iPD); SMA hypometabolism may be related to clinical characteristics (akinesia) of GBA-PD] | GBA-PD = findings consistent with moderately advanced iPD with cognitive impairment |
| Saunders-Pullman et al. | 2 GD-p | Age 54–58, UPDRS III/HY NA | Atypical features in both patients | GBA-PD = [PDPR (vs. LRRK2-PD and iPD); SMA hypometabolism may be related to clinical characteristics (akinesia) of GBA-PD] | GBA-NMC and GD = [binding potential in the SN (correlated with hyposmia), bilateral metabolism in putamino-occipital, anteromedial frontal, and temporal cortex] | GBA-PD = findings consistent with moderately advanced iPD with cognitive impairment |

| Microglial activation (11C-(R)-PK11195 binding potentials) |
|------------------|
| Mullin et al. | 5 GD, 4 GBA-NMC, 20 CTRL | Age GD = 62.6 ± 2.9, GBA-NMC = 63.3 ± 7, UPDRS III GD = 22.8 ± 10.4, GBA-NMC = 4.5 ± 2.4 | MoCA GD = 27.4 ± 19, GBA-NMC = 27.8 ± 2.2 | NA | GBA-NMC and GD = [binding potential in the SN (correlated with hyposmia), bilateral metabolism in putamino-occipital, anteromedial frontal, and temporal cortex] | GD and GBA-NMC = [microglial activity in brain regions susceptible to Lewy body formation—possibly cytoprotic or neuroprotective process] |

Abbreviations: PET, positron emission tomography; GBA-PD, Parkinson’s disease with GBA mutations/variants; iPD, idiopathic Parkinson’s disease; UPDRS III, Unified Parkinson’s Disease Rating Scale, Part III; MDS, Movement Disorder Society; BDII-II, Beck’s Depression Inventory, II; PDPR, PD-related pattern; PDCP, PD-cognitive pattern; GD-p, GBA-PD; LRRK2-PD, Parkinson’s disease with LRRK2 mutations; CTRL, controls; IC, inclusion criterion; MMSE, Mini-Mental State Exam; MDRS, Mattis Dementia Rating Scale; HY, Hoen and Yahr score; MoCA, Montreal Cognitive Assessment; SN, substantia nigra; 123-FP-CIT-SPECT, dopamine transporter 123-I iodoamphetamine single-photon emission computed tomography.
### Table 3: Brain perfusion imaging studies

| Studies | Technique | Sample | Clinical features | Cognition | Clinical findings | Imaging findings | Conclusions |
|---------|-----------|--------|-------------------|-----------|------------------|-----------------|-------------|
| Ichinose et al[^1][^2] | IMP-SPECT | 2 GBA-PD, 5 GBA-NMC | Age GBA-PD = 49.62; GBA-NMC = 49–77 | 1 GBA-PD = MCI | Only akinetic-rigid PD | 1 GBA-PD subject (with MCI) = ↓ perfusion in occipital lobes | GBA-NMC = no abnormal findings; 1 GBA-PD = occipital hyperperfusion |
| Cilu et al[^3][^4][^5] | Technetium-99m SPECT | 35 GBA-PD, 38 iPD, 32 DLB | Whole group Age GBA-PD = 64.3 ± 9.7, iPD = 69.4 ± 10.2, DLB = NA | MMSE GBA-iPD = 28.6 ± 1.3, PD = 28.6 ± 1.9, DLB = 19.4 ± 3.8 | GBA-PD = ↓ age at onset, MMSE, ↑ dementia (vs. iPD) | All GBA-PD = ↓ perfusion in posterior parietal and occipital lobes (vs. iPD); GBA-PD severe mutations = ↓ perfusion in parietal lobes (vs. GBA-PD mild mutations) | GBA-PD severe mutations = ↓ perfusion in posterior parietal and occipital lobes (vs. iPD); GBA-PD mild mutations = similar pattern to iPD |
| Oeda et al[^6][^7] | IMP-SPECT | 12 GBA-PD, 45 iPD | Whole group Age GBA-PD 58.9 ± 3.3, iPD = 61.0 ± 1.3 | MMSE GBA-iPD = 23.7, iPD = 25.8 | GBA-PD = ↑ dementia and psychosis (vs. iPD) | GBA-PD = ↓ perfusion in the bilateral parietal cortex, including the precuneus (vs. iPD) | GBA-PD = greater parietal perfusion dysfunction relative to iPD |
| Goker-Alpan et al[^8][^9] | H215O PET | 7 GD-p, 14 GD, 11 iPD, 7 GBA-NMC, 68 CTRL | Age GD-p = 56.6 ± 9.2, GD = 52.6 ± 12.4, iPD = 62.1 ± 7.1, GBA-NMC = 50.1 ± 18.0, UPDRS-III GD-p = 27.4 ± 8.2, iPD = 27.5 ± 10.5, HY GD-p = 2.4 ± 0.7, iPD = 1.9 ± 0.7 | IQ (WAIS) GD-p = 97.3 ± 8.4, iPD = 108.6 ± 35.6 | GD-p = ↑ right-sided symptoms than iPD | GD-p = ↓ perfusion in lateral parieto-occipital association cortex and precuneus bilaterally compared to CTRL and iPD | GD-p = greater parieto-occipital perfusion dysfunction relative to iPD |

Studies are ordered chronologically. If not specified, the studies are cross-sectional. Information on how controls and iPD were selected is provided in Supplementary Table S1. See Supplementary Table S1 for details of classification of GBA mutations/variants. When available, mean ± standard deviation is reported; otherwise, mean, range (separated by ->), single values (separated by comma), or inclusion criteria is reported. If no information is available, NA is reported. If details for the subgroup that underwent imaging study are not available, results for the whole group are reported.

[^1]: Retrospective-longitudinal study. Technetium-99m SPECT was performed once, after 8.3 ± 4.7 years from disease onset in GBA-PD, 8.3 ± 4.4 years in iPD, and 8.2 ± 3.5 years in DLB.
[^2]: Retrospective study. IMP-SPECT was performed once, after 7.3 ± 1.5 years from disease onset in GBA-PD and 7.1 ± 0.7 years in iPD.
[^3]: GBA-PD showed increased hazard ratios for dementia (8.3) and psychosis (3.3) versus iPD.

Abbreviations: IMP-SPECT, N-isopropyl-p-[123I]iodoamphetamine single-photon emission computed tomography; GBA-PD, Parkinson’s disease with GBA mutations/variants; GBA-NMC, nonmanifesting carriers of GBA mutations/variants; UPDRS III, Unified Parkinson’s Disease Rating Scale, Part III; HY, Hoehn and Yahr score; NA, not available; MCI, mild cognitive impairment; iPD, idiopathic Parkinson’s disease; DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Exam; PET, positron emission tomography; GD-p, GD with parkinsonism; GD, Gaucher’s disease; IQ, intelligence quotient; WAIS, Wechsler Adult Intelligence Scale; CTRL, controls.
### TABLE 4  Nigrostriatal imaging studies

| Studies                  | Sample                              | Clinical features                                                                 | Cognition                        | Clinical findings                                                                 | Imaging findings                                                  | Conclusions                                                                                |
|--------------------------|-------------------------------------|-----------------------------------------------------------------------------------|----------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| "[^18F]FDopa PET"        | 5 GD-p, 15 GD, 2 GBA-PD, 12 GBA-NMC | UPDRS III GD-p and GBA-PD = 26 ± 13, GD and GBA-NMC = 1 ± 2                      | NA                               | NA                                                                               | Inverse correlation between uptake and SN hyperechogenicity in GD-p and GBA-PD | Correspondence between transcranial sonography and [18F]FDopa PET only in GD-p and GBA-PD |
| Mullin et al[^2]         | 5 GD, 4 GBA-NMC, 9 CTRL             | Age GD = 62.6 ± 2.9, GBA-NMC = 63.3 ± 7, UPDRS III GD = 12.8 ± 10.4, GBA-NMC = 45 ± 2.4 | MoCA GD = 27.4 ± 1.9, GBA-NMC = 27.8 ± 2.2 | No patient had parkinsonism                                                     | Normal uptake in GD and GBA-NMC = † variance in uptake (vs. CTRL)                           | GD and GBA-NMC = † uptake might be a compensatory mechanism                               |
| Lopez et al[^3]         | Baseline                            | Age GD + GD-p = 56 ± 12, GBA-PD + GBA-NMC = 57 ± 12, UPDRS III/HY = NA            | NA                               | NA                                                                               | GD-p and GBA-PD = † striatal uptake (putamen) (vs. GD and GBA-NMC)          | GD-p and GBA-PD = findings consistent with iPD; no findings consistent with iPD            |
|                         | 11 GD-p, 26 GD, 4 GBA-PD, 16 GBA-NMC, 98 CTRL | 1.5 to 12 year follow-up                                                         | Only 1 GBA-NMC                  | Only 1 GBA-NMC developed parkinsonism                                              | GD-p and GBA-PD = † uptake, 4% per year in the caudate, 5% per year in the putamen (vs. baseline) | GD-p and GBA-PD = † uptake                                                               |
|                         | 11 GD-p, 26 GD, 4 GBA-PD, 16 GBA-NMC, 98 CTRL | 1.5 to 12 year follow-up                                                         | Only 1 GBA-NMC                  | Only 1 GBA-NMC developed parkinsonism                                              | GD-p and GBA-PD = † uptake, 4% per year in the caudate, 5% per year in the putamen (vs. baseline) | GD-p and GBA-NMC = † uptake                                                               |
|                         | 5 GD-p, 15 GD, 2 GBA-PD, 11 GBA-NMC, and 15 CTRL | 1.5 to 12 year follow-up                                                         | Only 1 GBA-NMC                  | Only 1 GBA-NMC developed parkinsonism                                              | GD-p and GBA-PD = † uptake, 4% per year in the caudate, 5% per year in the putamen (vs. baseline) | No relationship between [18F]FDopa uptake and prodromal features                          |
| Greuel et al[^1]        | 7 GBA-PD, 31 iPD                    | Whole group                                                                       | Dementia was excluded (MDS criteria) | GBA-PD = † global cognition z score[^b] | GBA-PD = † uptake in the bilateral caudate nuclei, anterioromedial putamen, and nucleus accumbens contralateral to the more affected body side (vs. iPD) | GBA-PD = more severe alterations vs. iPD, even in carriers without dementia                |
| Barrett et al[^2]       | 2 GBA-PD                            | Age = 39, 59, UPDRS I mentation score = 1, 0                                      | NA                               | NA                                                                               | GBA-PD = † striatal uptake in the bilateral caudate nuclei                  | GBA-PD = findings consistent with iPD                                                    |
| Goker-Alpam et al[^3]   | 7 GBA-PD, 14 GD, 11 iPD, 7 GBA-NMC, 68 CTRL | 70% were carriers without dementia                                                | IQ (WAIS)                       | IQ (WAIS)                                                                 | GBA-PD = † striatal uptake in the bilateral caudate nuclei                  | GBA-PD = findings consistent with iPD                                                    |
|                         | 7 GBA-PD                            | Age = 60, 54, UPDRS I/HY = NA                                                     | Cognitive dysfunction in both patients | More GD-p presented with right-sided symptoms than iPD | GD-p, GD, and iPD = † striatal uptake (>putamen) uptake                      | GD = † putaminal dopamine synthesis but effect driven by 2 subjects                      |
| Saunders-Pullman et al[^4] | 2 GBA-PD                           | Age = 60, 54, UPDRS I/HY = NA                                                     | Cognitive dysfunction in both patients | Anyypical features in 1 patient[^d] | In both = bilateral † striatal uptake                                         | GBA-PD = findings consistent with iPD                                                    |
| Krauss et al[^5]        | 2 GD-p                              | Age = 60, 54, UPDRS I/HY = NA                                                     | 1 had dementia                  | Anyypical features in one patient[^d] | In both = bilateral † striatal uptake                                         | GBA-PD = findings consistent with iPD                                                    |

(Continues)
| Studies | Sample | Clinical features | Cognition | Clinical findings | Imaging findings | Conclusions |
|---------|--------|-------------------|-----------|------------------|----------------|-------------|
| [123]I-FP-CIT-SPECT | | | | | | |
| Lee et al | 39 GBA-PD, 72 LRRK2-PD, 367 iPD, 213 CTRL (PPMI + 38 iPD and 71 CTRL (GSH cohort) | PPMI cohort | GBA-PD = 61.5 ± 112, LRRK2-PD = 62.0 ± 86, iPD = 60.9 ± 11.3, CTRL = 60.9 ± 11.3 | NA | GBA-PD = ⩾ UPDRS III (vs. iPD and LRRK2-PD), LRRK2-PD, and GBA-PD = ⩾ disease duration (vs. iPD) | GBA-PD = more rapid deterioration of putaminal dopaminergic function during the premotor phase |
| Caminiti et al | Baseline | 46 GBA-PD, 539 iPD (261 LO-iPD, 58 EO-iPD), 59 CTRL | Age GBA-PD = 58.9 ± 9.6, EO-iPD = 47 ± 4.8, LO-iPD = 64.8 ± 7.1, CTRL = 59.2 ± 10.7 | MoCA GBA-PD = 26.9 ± 2.5, EO-iPD = 28.1 ± 2.3, LO-iPD = 27 ± 2.3, CTRL >26 | No difference in binding (vs. iPD) GBA-PD = ⩾ UPDRS III, UPDRS total, SCOPA-AUT (vs. EO-iPD); ⩾ RBDSQ (vs. EO-iPD and LO-iPD); ⩾ MoCA (vs. EO-iPD) | GBA-PD = more widespread dopaminergic damage since the early phases; more aggressive clinical course |
| Baseline | 2-year follow-up | 22 GBA-PD, 146 iPD (127 LO-iPD, 19 EO-iPD), 59 CTRL | Age GBA-PD = 58.1 ± 7.5, EO-iPD = 47.2 ± 5.1, LO-iPD = 65.8 ± 7.5 | MoCA GBA-PD = 26.3 ± 3.7, EO-iPD = 27.3 ± 3.4, LO-iPD = 25.7 ± 3.3 | GBA-PD = ⩾ SCOPA-AUT (vs. EO-iPD) | In 2 years EO-iPD and LO-iPD reached the same dopaminergic damage severity as GBA-PD patients in the ventral striatum |
| Chung et al | 54 GBA-PD, 354 iPD | Age GBA-PD = 58.9 ± 9.5, iPD = 62.1 ± 9.6, MDS-UPDRS III GBA-PD = 222 ± 10.48 | MoCA GBA-PD = 27.2 ± 2.3 | GBA-PD = ⩾ MDS-UPDRS in the less affected side | No difference in binding (vs. iPD) | GBA-PD = reduced motor reserve (vs. iPD) |
| Sinunni et al | 184 GBA-NMC, 208 LRRK2-NMC, 194 CTRL | Age GBA-NMC = 61.8 ± 6, LRRK2-NMC = 61.6 ± 7, CTRL = 60.8 ± 11.3 | MoCA GBA-NMC = 26.8 ± 2.4, LRRK2-NMC = 26.8 ± 2.4, CTRL = 28.2 ± 1.1 | GBA-NMC and LRRK2-NMC = ⩾ MDS-UPDRS and SCOPA-AUT (vs. CTRL) | ⩾ Binding in 3% of GBA-NMC and 11% of LRRK2-NMC; GBA-NMC = ⩾ striatal binding ratio (vs. CTRL) | GBA-NMC and LRRK2-NMC = subtle motor and nonmotor signs before dopaminergic function deficit |

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### TABLE 4  
Continued

| Studies                        | Sample                          | Clinical features | Cognition                                                                 | Clinical findings                                                                 | Imaging findings                                                                 | Conclusions                                                                 |
|--------------------------------|---------------------------------|-------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Simoni et al<sup>30</sup>      | 80 GBA-PD, 158 LRRK2-PD, 31 iPD| Age = GBA-PD = 62.7 ± 9.9, LRRK2-PD = 63.8 ± 9.2, iPD = 63.8 ± 9.7, MDS-UPDRS III (OFF) GBA-PD = 26.2 ± 10.8, LRRK2-PD = 22.1 ± 11.6, iPD = 27.2 ± 11.1 | MoCA GBA-PD = 26.1 ± 2.9, LRRK2-PD = 25.9 ± 3.2, iPD = 26.2 ± 3.2 | GBA-PD = ↑ QuIP scores (vs. iPD); ↑ RBD6Q (vs. LRRK2-PD) | LRRK2-PD and GBA-PD = ↑ binding in the side contralateral to the more affected body side (vs. iPD) | GBA-PD and LRRK2 = slower decline in dopaminergic function |
| Ichihose et al<sup>10</sup>    | 2 GBA-PD, 4 GBA-NMC            | Age GBA-PD = 49, 62; GBA-NMC = 77–51 | MCI in 1 GBA-PD | NA | | 1384 |
| Chahine et al<sup>9</sup>      | 38 GBA-NMC, 88 LRRK2-NMC, iPD = 43, RBD = 39, hyposmia = 26 | Age GBA-NMC = 63.6 ± 7.5, LRRK2-NMC = 61.6 ± 7.1, iPD = 61.6 ± 9.7, RBD = 69.6 ± 5.5, hyposmia = 68.1 ± 6.2 | MoCA GBA-NMC = 27.6 ± 1.8, LRRK2-NMC = 25.6 ± 2.7, iPD = 27.1 ± 2.3, RBD = 25.3 ± 4.3, hyposmia = 27.3 ± 1.7 | GBA-NMC = ↓ MoCA and verbal memory (vs. LRRK2-NMC) | RBD = ↓ binding (vs. hyposmia and NMC) | Hyposmia = ↓ binding (vs. NMC) | No differences in GBA-PD (vs. other groups) | 123-FP-CIT-SPECT and GCase activity |
| Huertas et al<sup>31</sup>     | 298 PD (48 GBA-PD)             | NA                | 34 "probable dementia" and 25 "possible dementia" (MDS criteria)     | NA | GBA-PD (deleterious variants) = ↓ binding | GBA-PD (deleterious variants) = associated with ↓ striatal binding and ↑ progression to dementia |
| Cilia et al<sup>11</sup>       | 18 GBA-PD, 18 iPD, 14 DLB       | Whole group       | Age GBA-PD = 64.3 ± 9.7, iPD = 69.4 ± 10.2 | Dementia in 34.1% GBA-PD and 19.6% iPD | GBA-PD = younger age at onset (vs. iPD) | Binding iPD < GBA-PD < DLB | GBA-PD (severe mutation) = similar findings to DLB | GBA-PD (mild mutation) = similar findings to iPD |
| McNeill et al<sup>13</sup>     | 7 GBA-PD, 8 SNCA-PD, 3 LRRK2-PD, 12 PRKN-PD, 7 PINK1-PD | Age GBA-PD = 50 ± 13, SNCA-PD = 47.1 ± 7, LRRK2-PD = 51.5 ± 19.5, PRKN-PD = 44 ± 14, PINK1-PD = 42 ± 17, UPDRS III GBA-PD = 29.8 ± 5, SNCA-PD = 36.2 ± 14, LRRK2-PD = 30 ± 13, PRKN-PD = 28.2 ± 12.7, PINK1-PD = 12.8 ± 6 | No participant had cognitive impairment | PINK1-PD = ↓ UPDRS III (vs. other groups) | All groups = ↓ binding (vs. normal values) | GBA-PD and LRRK2-PD = ↑ asymmetry (vs. other genetic PD) | DAT asymmetry in GBA-PD and LRRK2-PD due to the need for interactions with additional genetic or environmental factors |
| Kono et al<sup>37,44</sup>     | 1 GD-p, 2 GBA-PD, 3 GBA-NMC    | Age GD-p = 38, GBA-PD = 71, GBA-NMC = 47–74, HY GD-p = 4, GBA-PD = 3 and 4 | MMSE GD-p = 24, GBA-PD = 24 | Only akinetic-rigid PD and 3 | GBA-NMC = 24–30 | Normal binding in all | GD-p and GBA-PD = findings consistent with iPD (see also 11 C-CFT PET) | |

(Continues)
| Studies                  | Sample                        | Clinical features | Cognition                   | Clinical findings | Imaging findings | Conclusions                                      |
|-------------------------|-------------------------------|-------------------|-----------------------------|-------------------|-----------------|-------------------------------------------------|
| Kraoua et al²⁶         | 2 GD-p                        | Age 41, 61        | 1 had dementia              | Atypical features in one patient³ | Normal binding in both | GD-p = findings consistent with iPD            |
|                         | UDPRIS III/HY NA              |                   |                             |                   |                 |                                                 |
| 11 C-CFT [β-carbomethoxy-β-(4-fluorophenyl) tropane] PET |                               |                   |                             |                   |                 |                                                 |
| Kono et al²⁷,²⁸         | 1 GD-p, 1 GBA-PD, 3 GBA-NMC  | Age GD-p = 38, GBA-PD 71, GBA-NMC = 47-74 | MMSE 1 GD-p = 24, GBA-PD = 24 and 30 | Only akinetic-rigid PD | GBA-NMC = ↓ caudate uptake | GD-p and GBA-PD = findings consistent with iPD |
|                         | HY GD-p = 4, GBA-PD = 3 and 4 |                  | GBA-NMC = 24-30            |                   |                 |                                                |
|                         | UPDRS III GD-p = 21, GBA-PD = 16 and 36 |         |                             |                   |                 |                                                |
| ¹⁸F-FP-CIT PET          |                               |                   |                             |                   |                 |                                                |
| Sunwoo et al²⁹          | 1 GD-p, 1 GBA-PD             | Age GD-p = 44, GBA-PD = 55 | GBA-PD = no cognitive impairment, GD-p = NA | Both = ↓ uptake in the posterior putamen | GDA-P and GBA-PD = findings compatible with iPD |                                                 |
|                         | UPDRS III GD-p = 12, GBA-PD = 25 |                   |                             |                   |                 |                                                |

Studies are ordered chronologically. If not specified, the studies are cross-sectional. Information on how controls and iPD were selected is provided in Supplementary Table S1. See Supplementary Table S1 for details of classification of GBA mutations/variants. When available, mean ± standard deviation is reported; otherwise, mean, range (separated by -), single values (separated by comma), or inclusion criteria is reported. If no information is available, NA is reported. If details for the subgroup that underwent imaging study are not available, results for the whole group are reported.

*Longitudinal study. The study has been divided into two parts for clarity in the table; the second line refers to the longitudinal analysis, range 1.5- to 12-year follow-up.

*A cognitive test battery covered the following domains: executive function, memory, attention, language, and visual-spatial abilities, from which a global cognition Z score was computed using age- and education-adjusted standard norms. The global cognition Z-score was significantly lower when the BDI-II score was included as a covariate.

*The patient showed fluctuations in attention and memory, moderate letter fluency difficulties, mild bradyphrenia, executive dysfunction, and spatial processing deficits.

*The patient showed minimal response to levodopa and dementia within 3 years of parkinsonism onset with visuoconstructive apraxia and hallucinations.

*Longitudinal study (<5-year follow-up). Dopaminergic function before onset of deterioration was estimated by applying a linear model for PD subjects.

*Subjects from the PPMI cohort.

*Longitudinal study. The study has been divided into two parts for clarity in the table; the second line refers to the longitudinal analysis, up to ~2-year follow-up (imaging data available).

*Retropective study (1 year), all patients underwent [¹²³I]FP-CIT SPECT after 6 ± 6 years from disease onset.

Abbreviations: GD-p, GD with parkinsonism; GD, Gaucher’s disease; GBA-PD, Parkinson’s disease with GBA mutations/variants; GBA-NMC, nonmanifesting carriers of GBA4 mutations/variants; DLB, dementia with Lewy bodies; UPDRS III, Unified Parkinson’s Disease Rating Scale, Part III; HY, Hoehn and Yahr score; NA, not available; SN, substantia nigra; CTRL, controls; MoCA, Montreal Cognitive Assessment; IPD, idiopathic Parkinson’s disease; MDS, Movement Disorder Society; BDHI-II, Beck’s Depression Inventory, II; IQ, intelligence quotient; WAIS, Wechsler Adult Intelligence Scale; SPECT, single-photon emission computed tomography; LRRK2-PD, Parkinson’s disease with LRRK2 mutations; PPMI, Parkinson’s Progression Markers Initiative; LO-IPD, early-onset idiopathic Parkinson’s disease; EO-IPD, early-onset idiopathic Parkinson’s disease; SCOPA-AUT, Scale for Outcomes in Parkinson’s Disease-Autonomic; RBDSSQ, REM Sleep Behavior Disorder Screening Questionnaire; MDS-UPDRS III, Movement Disorder Society-sponsord revision of the Unified Parkinson’s Disease Rating Scale, Part III; LRRK2-NMC, non-manifesting carriers of LRRK2 mutations/variants; MCI, mild cognitive impairment; GCae, glaucocebroadie; RBD, REM sleep behavior disorder; SNCA-PD, Parkinson’s disease with SNCA mutations/variants; PINK1-PD, Parkinson’s disease with PINK1 mutations/variants; PRKN-PD, Parkinson’s disease with PRKN mutations/variants; DA, dopamine transporter; MMSE, Mini-Mental State Exam; [¹⁸F-FP-CIT PET, ¹⁸F-fluoropropylcarbochromoxydophenyltropane positron emission tomography; GSH, Gangnam Severance Hospital; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease.
no patient presented dementia or hallucinations, reduced functional connectivity in the parieto-occipital cortex was found in GBA-PD relative to iPD, similar to dementia with Lewy bodies (DLB) patients and PD with visual hallucinations.

**Positron Emission Tomography with 2-\textsuperscript{18}F-Fluorodeoxyglucose**

Five studies were included (Supplementary Table S1 and Table 2).

Fluorodeoxyglucose positron emission tomography (FDG-PET) is widely used for the evaluation of cortical glucose metabolism in several neurodegenerative disorders. In PD, FDG-PET shows two distinct covariance patterns on resting state: the PD-related-pattern (PDRP), associated with disease progression and motor symptoms, and the PD-cognitive pattern (PDCP), associated with cognitive dysfunction.\textsuperscript{14} A study\textsuperscript{23} reported increased PDRP scores and a trend for increased PDCP score (in line with a trend in worse cognitive function) in GBA-PD compared to matched iPD. Similarly, in another study,\textsuperscript{25} despite matched motor impairment, the GBA-PD group showed higher PDRP scores than iPD and LRRK2-PD. Moreover, GBA-PD was the only group to show elevated PDCP expression compared to controls (despite not having dementia). Using graph theory, the authors found that even though GBA-PD, LRRK2-PD, and iPD express the same disease-specific networks, information flow through these metabolic networks differs across patient groups.\textsuperscript{25} LRRK2-PD showed increased functional connectivity within the metabolically active PDRP core zone, and preferential gain in connectivity within the PDRP core was associated with lower disease network expression, indicating less-severe underlying functional pathology in PD patients carrying this mutation. By contrast, in GBA-PD the gains in connectivity extend outside the core, along with increased expression of the whole network. LRRK2-PD showed more connections within the core and GBA-PD within the periphery, suggesting that the PDRP “weather front” has progressed less in LRRK2-PD and more in GBA-PD, over the same disease duration. These findings seem consistent with a more aggressive natural history in GBA-PD.

Some other reports of FDG PET are available, although, due to the small samples, it is difficult to draw any conclusion from the results (Table 2).\textsuperscript{26-28}

**Microglial Activation Studies**

One study was included (Supplementary Table S1 and Table 2). Inflammation is known to play an important role in the pathogenesis of GD, and it is considered to contribute to the neurodegenerative process in PD.\textsuperscript{52} A study,\textsuperscript{29} using 11C-(R)-PK11195 PET, demonstrated increased microglial activation in brains of GD patients without Parkinsonism and GBA-NMC compared to controls in the SN, occipital and temporal lobes, cerebellum, hippocampus, and mesencephalon. There was a correlation between the degree of hyposmia and nigral microglial activation. The same study evaluated (see later), showing no differences between carriers and noncarriers. The authors suggest that a biphasic trajectory of microglial activation and dopaminergic degeneration might explain the different results.\textsuperscript{29}

**Brain Perfusion Studies**

Four studies were included (Supplementary Table S1 and Table 3).

Cerebral perfusion studies evaluate the metabolic status of brain tissue by quantifying changes in the regional cerebral blood flow using various radiotracers.\textsuperscript{14}

In one study,\textsuperscript{31} GBA-PD with severe mutations showed reduced posterior parietal and occipital blood perfusion compared to iPD, similar to DLB; conversely, GBA-PD with mild mutations showed a similar pattern to iPD. Additional analysis performed after excluding patients with dementia yielded similar results. This is in line with other findings from this study,\textsuperscript{31} which demonstrated that the risk for dementia is influenced by the type of GBA mutation/variant. Another study\textsuperscript{32} reported reduced regional cerebral blood flow in the bilateral parietal cortex, including the precuneus, in GBA-PD compared to sex-, age-, and disease-duration-matched iPD subjects. Occipital hypoperfusion, resembling the DLB pattern, was reported in a PD member of a family with a gross GBA deletion; 6 other individuals (1 GBA-PD and 5 GBA-NMC) displayed normal findings.\textsuperscript{30} A study described a reduced regional cerebral blood flow in GD-p in both inferior parietal lobules and the precuneus of both hemispheres but sparing the posterior cingulate gyrus,\textsuperscript{33} this pattern is typical of DLB.\textsuperscript{33}

**Nigrostriatal Imaging**

Twenty-one studies were included (Supplementary Table S1 and Table 4).

[\textsuperscript{18}F]FDopa PET is used to assess the density of presynaptic nigrostriatal axons.\textsuperscript{14} [123I]N-\textomega-fluoropropyl-2β-carbomethoxy-iodophenyl nortropane ([123I]FP-CIT) single photon emission computed tomography (SPECT) evaluates nigrostriatal integrity by measuring the density of dopamine transporters (DATs) located at the presynaptic nigrostriatal terminals.\textsuperscript{14} Other techniques, such as C11-Raclopride PET, 11 C-CFT [2β-carbomethoxy-3β-(4-fluorophenyl) tropaene] PET, and \textsuperscript{18}F-FP-CIT PET, can be used to investigate the integrity of the nigrostriatal system.\textsuperscript{14}

**6-\textsuperscript{[18]F}fluoro-L-Dopa ([\textsuperscript{18}F] FDopa) PET**

A study compared the [\textsuperscript{18}F]FDopa PET and transcranial sonography (TCS) findings in subjects with
GBA mutations (homozygous and heterozygous) with and without parkinsonism (GP-d and GBA-PD vs. GD and GBA-NMC), showing an inverse relationship between [(18)F]-FDOPA uptake and nigral echogenic areas only in subjects with parkinsonism. The same authors, in a longitudinal study (1.5–12 years), demonstrated a lack of progression both radiologically and clinically—in terms of parkinsonism—in a cohort of GBA-NMC (even with familiarity for PD or DLB). On the contrary, as expected, GBA-PD and GD showed decreased binding over follow-up, especially in the putamina. In the GBA-NMC cohort, only 1 subject aged 60 years (carrying an N370S mutation) developed signs of PD: [(18)F]FDopa PET scan and TCS performed 1 year before the onset were unremarkable. In a study, compared with iPD, GBA-PD showed a greater reduction in [(18)F]FDopa uptake in the bilateral caudate nuclei, anteromedial putamen ipsilateral, and nucleus accumbens contralateral to the more affected body side. Together with other findings (see the PET and MRI sections), this led the authors to conclude that GBA-PD has a more aggressive course than iPD. Finally, in another study, GBA-NMC and GD showed a similar mean striatal [(18)F]dopa uptake to healthy controls, although with a greater variance—with some subjects displaying higher dopamine binding values. Whether this finding represents a compensatory mechanism is not known. A bilaterally reduced uptake in the striatum has also been reported in GD without parkinsonism in one study, although the authors noted that this effect was attributable to 2 patients (of 14) with reduced uptake.

Other reports describe similar findings to iPD in GBA-PD or GD-p33,36 (see Table 4).

[123]I-n-ω-fluoropropyl-2β-carbomethoxyiodophenyl nortropane ([123I]FP-CIT) SPECT

Among a cohort including both GBA-NMC and LRRK2-NMC, a minority of subjects displayed DAT deficit (3% of GBA-NMC vs. 11% of LRRK2-NMC). GBA-NMC rather showed increased DAT striatal binding ratios compared with controls in the caudate, putamen, and striatum: this finding was interpreted as a possible compensatory mechanism in the preclinical stage. Clinically, compared with controls, both GBA-NMC and LRRK2-NMC showed subtle motor and nonmotor signs (a possible bias in evaluation due to the lack of binding to the genetic status must be pointed out). A study compared cohorts at risk for PD (namely REM-sleep behavior disorder [RBD], hyposmia, GBA-NMC, and LRRK2-NMC) from the PPMI: a lower mean striatal binding ratio was observed in RBD compared to the hyposmia and NMC cohorts. No difference was observed between GBA-NMC and LRRK2-NMC.

In one study both GBA-PD and LRRK2-PD showed higher (better) striatal binding ratio in the caudate and putamen contralateral to the more affected body side when compared with iPD. As a possible explanation for this finding, the authors suggest a slower rate of decline in DAT in genetic PD compared to iPD or a disruption of dopamine release before the loss of dopaminergic terminals (leading to an overestimation of DAT binding). In this study, GBA-PD showed similar motor and nonmotor symptoms (except for impulse control disorder) to iPD. Conversely, another study reported more pronounced dopaminergic dysfunction in GBA-PD than iPD: age-adjusted analysis showed similar DAT density between GBA-PD with mild mutations and iPD and between GBA-PD with severe mutations and DLB, in line with other findings from the same study. The discrepancy between the two studies could be associated with the different mutations included. In fact, in the study by Simuni et al, most of the cohort carried the N370S mutation, which is a mild mutation: as demonstrated by Cilia et al, and confirmed by a recent meta-analysis, patients with this mutation show similar cognitive features to iPD.

One longitudinal study showed a faster clinical and cognitive deterioration, as well as a more diffuse striatal and extra-striatal damage, in GBA-PD relative to iPD.17 The clinical and radiological progression in GBA-PD was similar to that in LO-iPD rather than EO-iPD, leading the authors to hypothesize a biological role of GBA in the pathogenesis of the “malignant PD phenotype,” a more aggressive form of disease associated to LO-iPD (see the MRI section). In another study, the temporal trajectory for putaminal dopaminergic deficit during the premotor period (10 years) in PD patients was modeled using extensive longitudinal PPMI data: according to this model, patients carrying the N370S GBA mutation have more rapid deterioration in dopaminergic function in the premotor phase.

In one study, GBA-PD showed a more asymmetric DAT deficit compared to PD patients carrying other mutations with higher penetrance (eg, SNCA). The authors hypothesized that this finding, which resembles what is observed in iPD, suggests that other genetic or environmental factors are needed to drive dopaminergic neuronal loss in GBA-PD.

In another study, despite similar levels of DAT binding compared with other PD patients, GBA-PD showed more severe motor signs in the less-affected side (despite similar levels of DAT availability in the contralateral putamen): this finding has been reconfigured to a lower “motor reserve” in GBA-PD that could contribute to a more severe phenotype.

A study investigating the role of genetic variants (APOE e2 and e4 alleles, MAPT H1 and H2 haplotypes, COMT Met allele, SNCA G allele, and deleterious
| Studies            | Sample            | Clinical features | Cognition | Clinical findings | Imaging findings | Conclusions                                                                 |
|--------------------|-------------------|-------------------|-----------|-------------------|------------------|-----------------------------------------------------------------------------|
| Eisenberg et al    | 5 GD-p, 2 GBA-PD, 15 GD, 12 GBA-NMC | UPDRS II GD-p and GBA-PD = 26 ± 13, GD and GBA-NMC = 1 ± 2 | NA        | NA                | GD-p and GBA-PD = ↑ SNh (vs. GD and GBA-NMC)                                | GD-p and GBA-PD = TCS findings consistent with iPD Normal TCS in the absence of parkinsonism |
| Lopez et al        | 9 GD siblings' paroxysms disorder for parkinsonism (5 GD-p + 1 GD-HDB, 9 GD) | Age GD-p = 57.2, GD = 57.7 UPDRS III GD-p = 27.18, GD = 5.14 | WAIS = no difference (GD-p vs. GD) | GD-p = ↑ UPDRS III, hypomnesia, urinary dysfunction (vs. GD)               | GD-p = ↑ SNh (vs. GD) TCS findings consistent with iPD Normal TCS in the absence of parkinsonism |
| Arkaiky et al      | 11 GBA-PD, 130 GD, 68 GBA-NMC, 43 CTRL | Age GBA-PD = 58 (49–74), GD = 51 (40–80), GBA-NMC = 51 (40–77), CTRL = 51 (40–73) UPDRS II/HY NA | NA        | NA                | GBA-PD, GD, GBA-NMC = ↑ SNh (vs. CTRL) GBA-PD and NMC = ↑ SNh also in the absence of parkinsonism No correlation with glucosylphosphatase levels |
| Omran et al        | 26 GBA-NMC, 26 CTRL | Age GBA-NMC = 35.6 ± 6.9, CTRL = 34.92 ± 10.14 UPDRS II/HY NA | MMSE GBA-NMC = 28.8 ± 0.6, CTRL = 30 ± 0 | NA                | GBA-NMC = ↑ SNh (vs. CTRL) GBA-NMC = ↑ third ventricle width (vs. CTRL) GBA-NMC = ↑ SNh and third ventricle width also in the absence of parkinsonism |
| Bötzler et al      | 5 GD-p, 11 GD, 12 iPD, 32 CTRL | Age GD-p = 52.6 ± 8.0, GD = 46.4 ± 11.4, iPD = 60.9 ± 4.1, CTRL = 48.2 ± 11.7 UPDRS II GD-p = 29.6 ± 21.5, GD = 0.3 ± 0.5, iPD = 19.9 ± 8.5, CTRL = 0.5 ± 1.1 | Executive dysfunction (TMT-B score) in 4% GD and GD-p, 83% iPD, 3% CTRL | GD-p = ↑ hypomnesia, motor signs, NMS (vs. GD), GD and GD-p = ↑ executive dysfunction, motor signs, depression (vs. CTRL), GD and GD-p = ↑ executive dysfunction, motor signs and NMS (vs. iPD) | GD and GD-p = ↑ SNh and ↓ brainstem raphe hypoechogenicity (vs. CTRL), GD and GD-p = ↑ third ventricle width (vs. iPD); no differences between GD-p and GD |
| Kesogević et al    | 4 GD-p, 12 GD, 18 GBA-PD, 32 iPD, 9 GBA-NMC, 43 CTRL | Age GD-p = 49.0 ± 12.1, GD = 44.7 ± 19.0, GBA-PD = 62.6 ± 8.6, iPD = 61.5 ± 9.3, GBA-NMC = 56.7 ± 11.7, CTRL = 54.5 ± 14.9 UPDRS II GD-p = 47.2 ± 27.7, GBA-PD = 38.6 ± 21.4, iPD = 35.9 ± 15.3, HY GD-p = 2.5 ± 12.2, GBA-PD = 2.7 ± 11, iPD = 2.4 ± 0.8 | MMSE GBA-PD = 28.5 ± 13.3, GBA-PD = 27.9 ± 2.6, iPD = 28.5 ± 2.4 | GD = ↑ anxiety (vs. GBA-PD and iPD) GD-p, GBA-PD, iPD = ↑ SNh (vs. GBA-NMC and CTRL) No difference in third ventricle width | GD-p and GBA-PD = TCS findings consistent with iPD |
| Barrett et al      | 4 GD-p, 23 GBA-PD, 27 LRRK2-PD, 4 GBA + LRRK2-PD, 32 iPD, 30 CTRL | Age GD-p = 60.2 (50.2–67.6), GBA-PD = 65.0 (99.0–68.2), PD-LRRK2 het = 68.2 (61.6–74.5), PD-LRRK2 het = 64.4 (62.7–66.2), GBA + LRRK2-PD = 65.3 (63.4–68.0), iPD = 64.8 (59.5–73.8), CTRL = 60 (51–68) UPDRS III GD-p = 32 (22–33), GBA-PD = 19 (14–25), PD-LRRK2 het = 11 (8–11), PD-LRRK2 het = 12 (13–14), GBA + LRRK2-PD = 18 (16–19) iPD = 19 (15–24) | NA | GD-p, GBA-PD, iPD = ↑ UPDRS III (vs. LRRK2) GD-p, GBA-PD, LRRK2-PD, GBA + LRRK2-PD, iPD = ↑ SNh (vs. CTRL) No difference between GD-p, GBA-PD, LRRK2-PD, GBA + LRRK2-PD, iPD | GD-p, GBA-PD, LRRK2-PD = TCS findings consistent with iPD |

(Continues)
| Studies | Sample | Clinical features | Cognition | Clinical findings | Imaging findings | Conclusions |
|---------|--------|-------------------|-----------|------------------|-----------------|-------------|
| Brockmann et al. 20 | GBA-PD, 20 iPD | Age GBA-PD = 62.7 ± 10.4, iPD = 67.6 ± 9.3 | MoCA | GBA-PD = | GBA-PD = | GBA-PD = TCS findings consistent with iPD |
| | | UPDRS III GBA-PD = 34.7 ± 14.1, iPD = 27.8 ± 7.5, HY GBA-PD = 2.6 ± 0.9, iPD = 2.3 ± 0.5 | GBA-PD = cognitive impairment, psychiatric symptoms, NMS | TCS feature reported in 3 of 3 GBA-PD patients | Contrast imaging of SN hypoechogenicity; no difference in SNh | Brainstem raphe hypoechogenicity might underlie NMS |
| Saunders-Pullman et al. 21 | GD-p, 23 iPD, 40 CTRL | Age GD-p = 54.5, 65, iPD = 52 (35–79), CTRL = 47.5 (40–70) | Cognitive impairment reported in 3 of 3 GD-p patients | GD-p = SNh (vs. CTRL) | No differences between GD-p and iPD | GBA-PD = TCS findings consistent with iPD |

Studies are ordered chronologically. If not specified, the studies are cross-sectional. Information on how controls and iPD were selected is provided in Supplementary Table S1. See Supplementary Table S1 for details of classification of GBA mutations/variants. When available, mean ± standard deviation is reported; otherwise, mean, range (separated by –), single values (separated by comma), or IC is reported. If no information is available, NA is reported. If details for the subgroup that underwent imaging study are not available, results for the whole group are reported. Longitudinal study (range 1.5–12 year clinical follow-up). TCS was performed cross-sectionally. 

1 One patient showed medication sensitivity; progressive cognitive deterioration with cognitive fluctuations; and prominent deficits in spatial processing, semantic language, and attention; the other patient showed fluctuations in attention and memory, moderate to severe difficulty in self-feeding, handwriting, executive dysfunction, and spatial processing deficits. 

Abbreviations: GD-p, GD with parkinsonism; GBA-PD, Parkinson’s disease with GBA mutations/variants; GD, Gaucher’s disease; GBA-NMC, nonmanifesting carriers of GBA mutations/variants; UPDRS III, Unified Parkinson’s Disease Rating Scale; Part III, NA, not available; SNh, substantia nigra hypoechogenicity; TCS, transcranial sonography; DLR, dementia with Lewy bodies; WMH, White Matter Hyperintensities; iPD, idiopathic Parkinson’s disease; CTRL, controls; HY, Hoehn and Yahr score; MMSE, Mini-Mental State Exam; TMT-B, Trail Making Test B; NMS, nonmotor symptoms; het, heterozygous; hom, homozygous; LRRK2-PD, Parkinson’s disease with LRRK2 mutations; LRRK2-NMC, nonmanifesting carriers of LRRK2 mutations; GBA + LRRK2-PD, Parkinson’s disease with GBA mutations/variants and LRRK2 mutations; MoCA, Montreal Cognitive Assessment; IC, inclusion criteria.

and non-dopaminergic degeneration in GBA) in dopaminergic and non-dopaminergic degeneration in Parkinson’s disease (the so-called dopaminergic and non-dopaminergic syndrome hypothesis, that distinguishes dopaminergically mediated frontostriatal executive impairment and non-dopaminergically mediated visuospatial deficits). Studies using other techniques, that is, 11C-Raclo PET, 13C-FDC PET and Table 5. Transcranial Sonography

Nine studies were included (Supplementary Table S1 and Table 5).
alteration in the serotonergic system—is associated with depression and other psychiatric symptoms in PD and other neurological diseases. In this study, this result was in line with clinical data, which showed more depression and distinct autonomic disturbances in GBA-PD than iPD, leading the authors to suggest that imaging characteristics assessed with TCS might represent sonographic markers corresponding to some of these clinical findings. In another study, a higher prevalence of abnormal TCS raphe signals was found in GBA-PD compared to iPD (55.6% and 28.6% of patients, respectively), but it did not reach the level of statistical significance.

No study has found any difference in TCS findings based on the type of mutation or heterozygosity/homozygosity. 

**Multiomics Approach to Disentangle the Pathophysiology of GBA-PD**

The abnormal aggregation of misfolded neurotoxic proteins, such as α-synuclein, is a key pathological feature of PD. The mechanisms of the deposition of misfolded proteins in the disease epicenter and spread to large-scale network dysfunction through synaptic connections remain unknown; recent advances demonstrated that progression of PD might be a multifactorial process depending on regional vulnerability and cell-to-cell spreading of misfolded proteins. Temporospatial patterns of neuronal dysfunction, consequence of selective regional vulnerability and pathological spreading, might potentially explain different clinical features and progression in the GBA-PD relative to iPD. Using an agent-based epidemic spreading model to integrate structural connectivity, functional connectivity, and regional gene expression to predict sequential volume loss due to neurodegeneration, a recent study demonstrated that regional expression of GBA, together with SNCA, is a key player in the modulation of local regional vulnerability and is related to the development of atrophy. These findings are in line with biological evidence supporting the role of GCase in influencing α-synuclein synthesis, seeding, and clearance, which underlie the mechanism by which mutations/variants in GBA might affect the spread of protein aggregation and, consequently, be associated with faster disease progression. 

**Discussion**

The implication of GBA mutations/variants in the risk and progression of PD has opened new paths to understanding the mechanisms of PD and design potential therapeutic strategies. Although GBA-PD patients cannot clinically be recognized from patients without GBA variants/mutations, they undergo a more aggressive progression and carry a higher risk of cognitive impairment: imaging findings that are able to detect this evolution before its clinical manifestation are critical not only for their prognostic implications but also to elucidate the pathophysiology of the disease.

**Summary**

Most studies assessing the integrity of the nigrostriatal system failed to find any deficits in GBA-NMC or GD versus controls corroborating the hypothesis that GBA-mediated genetic risk alone does not determine an appreciably lower striatal dopaminergic tone. Similarly, no difference in nigrostriatal imaging has been consistently reported between GBA-PD or GD-p and other PD patients, rather contrasting findings—ranging from a diminished  to an augmented dopaminergic tone—have been reported. The differences among the studies, eg, differences in sample sizes, stage of PD, and mutations analyzed, might be accountable for these apparently confounding results although, overall, current evidence does not suggest the existence of a “nigrostriatal signature” of GBA mutations/variants in PD.

More insights from longitudinal studies demonstrated that GBA-PD show a more advanced disease at both structural MRI and 123-FP-CIT-SPECT imaging, which is reached by iPD after 5 and 2 years, respectively. Importantly, the trajectory of worsening of imaging features corresponded to a more aggressive clinical worsening, in both motor and nonmotor features. Similarly, brain perfusion and FDG-PET studies suggest a more aggressive underlying disease in GBA-PD, supporting the hypothesis that patients with GBA mutations seem to localize midway in the spectrum between PD and DLB, depending on the mutation. The greater involvement of the posterior cortical regions in GBA-PD compared to iPD could represent the neuroimaging counterpart of clinical findings reporting cognitive impairment as a major feature of GBA-PD. On the contrary, it must be noticed that most of these studies also reported worse cognitive function in this population compared to the control group and, thus, this difference might have influenced the imaging results.

Overall, studies in GBA-NMC have yielded highly heterogeneous—if not contrasting—results and overall do not allow to draw firm conclusions. It must be considered that the penetrance of GBA mutations is far from complete and depends on many factors, including the type of mutation and other genetic and non-genetic modifiers, most of which are unknown. Therefore, findings in these subjects might represent a mere correlate of their genotype not corresponding to the future development of PD: to effectively distinguish GBA-NMC between “healthy” and “prodromal” carriers and identify the mechanisms of GBA-PD
pathogenesis, longitudinal studies should evaluate the meaning of findings in NMC in relation to the risk of developing PD (eg, use of the MDS prodromal likelihood ratio scores as well as exposure to other environmental factors that contribute to PD in addition to the genetic status.65).

Limitations

As discussed, only a few studies included in the present review had a prospective design.

Other limitations hinder drawing results from the available studies. First, the variability in the approaches used across the studies to screen GBA and other PD-related genes may have significantly influenced the results. The techniques used to analyze genetic alterations were not uniform, with some studies investigating only specific mutations in GBA (eg, N370S and L444P, only GD-associated, only non-GD-associated) and other genes (eg, G2019S for LRRK2), whereas others assessed several known mutations and performed the sequencing of the entire GBA gene. Some studies excluded patients with other known mutations, whereas other studies did not assess other mutations at all. Moreover, a great heterogeneity was present in the control groups, as only in some studies were “controls” or “iPD” groups effectively tested for GBA mutations and information on genetic screening was missing, inherently flawing the comparison. Supplementary Table S1 summarizes the heterogeneity of the genetic assessment through the included studies. Other factors that may confound the results of the studies include heterogeneous cohorts with respect to the size, demographic data, and enrollment criteria of patients.

The complexity of interpreting the findings in GBA-NMC is increased by the overlap with other prodromal symptoms. RBD is of particular interest due to the significant risk of developing synucleinopathies that it carries.65 Neuroimaging findings in RBD have been extensively reviewed elsewhere; we refer the interested reader to a recent review on the topic.66

In addition, it must be noted that many studies used data from the PPMI cohort and analyzed the same subset of patients. Therefore, some data might be redundant rather than adding new information.

Finally, it is considered that “brain reserve”—a construct that combines the structural properties of the brain and cognitive skills and abilities that serve as a hedge against loss of function—influences the progression of PD and other neurodegenerative diseases (for review, see reference 68) but, besides the hypothesis of a reduced motor reserve in GBA-PD, little is known regarding its role in the pathogenesis of GBA-PD. Further research in this direction is warranted in the field of GBA-PD and GBA-NMC (as well as in other preclinical populations) to further elucidate the mechanisms of disease.

Conclusions

In conclusion, so far, in the field of GBA-related parkinsonism and its clinical, neuroimaging, and pathogenic features, simple solutions have been elusive: in the past decade, the increasing understanding of PD pathogenesis and clinical manifestations, the improvement in neuroimaging techniques, and the advances in basic sciences have led to a vertiginous increase in knowledge in the field of GBA-related PD, increasing the complexity of the problem rather than simplifying it. In parallel with clinical observations, current evidence in neuroimaging suggests a faster progression in GBA-PD, although the details of such progression (eg, the pathogenesis, pattern of progression, which tools are better to capture it, and which patients are at higher risk) must be determined. Cognitive impairment, a “clinical signature” of GBA-PD, seems to find its neuroimaging correlate in the greater cortical burden displayed by these patients as compared to other forms of PD. Undoubtedly, as extensively discussed, these aspects have been systematically investigated, whereas others might have been overlooked, and uneven matching of samples might account for some of these findings. Further studies implementing molecular imaging of protein accumulation, structural and functional connectivity, genetic expression profile, and the activity-related metabolic demand of specific brain regions will play a central role in the definition of vulnerability and understanding the progression of the disease, from the preclinical to the advanced stages, to identify pathogenic processes and cerebral regions implicated in the different and multifarious manifestations of PD.58 Larger, international, studies with better trail design, exploring more genetic variants, and with a longitudinal design are warranted to achieve a complete scenario of how the most common factors might contribute to the observed clinical and neuroimaging profile of GBA-PD patients, to uncover neurodegeneration mechanisms and to allow the development of new therapeutic strategies.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.