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TITLE: Exploring the link between GBA1 mutations and Dementia with Lewy bodies, A Mini-Review

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List of abbreviations: DLB, dementia with Lewy bodies; GCase, glucocerebrosidase; LB, Lewy body; SNCA, α-synuclein; PD, Parkinson's disease

ABSTRACT

Importance: Dementia with Lewy bodies (DLB) is a neurodegenerative disease linked to abnormal accumulation of phosphorylated α-synuclein. GBA1 is the gene encoding the lysosomal enzyme glucocerebrosidase (GCase), whose mutations are a risk factor of DLB.

Objective: To report all available data exploring the association between GBA1 mutations and DLB.

Evidence Review: All publications focused on GCase and DLB in humans between 2003 and 2022 were identified on PubMed, Cochrane and ClinicalTrials.gov.

Findings: 29 studies were included and confirmed the strong association between GBA1 mutations and DLB (Odds Ratio [OR]: 8.28). GBA1 mutation carriers presented a more malignant phenotype, with earlier symptom onset, more severe motor and cognitive dysfunctions, more visual hallucinations and rapid eye movement sleep disorder. GBA1 mutations were associated with "purer" neuropathological DLB. No therapeutic recommendations exist and clinical trials targeting GCase are just starting in DLB patients.

Conclusions and Relevance: This review reports a link between GBA1 mutations and the DLB phenotype with limited evidence due to the small number of studies.

Keywords: Dementia with Lewy bodies, Glucocerebrosidase, GBA1 gene, Gaucher disease

INTRODUCTION

Dementia with Lewy Bodies (DLB) is the second most common cause of neurodegenerative dementia, accounting for 10% to 15% of all cases[1] and belongs to the group of Lewy body (LB) diseases including Parkinson's Disease, DLB and multi-system atrophy. LB are intraneuronal proteinaceous inclusions composed of abnormal aggregates of phosphorylated α-synuclein (SNCA) in the nervous system.[2] According to the criteria, DLB patients suffer from neuropsychiatric symptoms, motor symptoms of parkinsonism as well as fluctuations, excessive daytime somnolence and sleep disorders.

The lysosomal enzyme glucocerebrosidase (GCase) is responsible for the breakdown of glucocerebroside into glucose and ceramide. Homozygous mutations in the GCase gene GBA1 cause GCase deficiency leading to glucocerebroside accumulation inside the lysosome. This accumulation results in Gaucher disease, the most frequent lysosomal storage disorder.[3] Since several patients with Gaucher disease present with parkinsonism and have GBA1 mutation-carrier relatives with Parkinson's disease (PD), subsequent studies have revealed that GBA1 mutations are associated with PD and with DLB.[4–8] GBA1 mutations causing Gaucher disease have been categorized as "severe" (L444P, for example) or "mild" (N370S, for example) based on their contribution to the phenotype of GD among homozygotes.[9] It has also been shown that the severity of the PD phenotype is related to the severity of the mutation in the GBA1 gene.[10,11]

Most previous reviews have focused on characterizing GBA1-associated PD, but, to the best of our knowledge, no review has yet summarized clinical research evidence in GBA1-associated DLB, including epidemiology, neuropathology, fluid biomarkers as well as clinical characteristics. This review will highlight current clinical research linked to GBA1 mutations, GCase activity and DLB, that may yield new therapeutic strategies.

METHODS

This systematic review was conducted according to PRISMA guidelines.[12] All published articles between January 1, 2003, and April 1, 2022, were identified on PubMed and Cochrane using the Medical Subject

Heading (MeSH) terms ("glucocerebrosidase" OR "GBA") AND ("Lewy body OR "Lewy bodies"). In addition, the ClinicalTrials.gov database was searched using the same search terms. Additional studies were included from the reference lists of relevant studies. Studies were included if they focused on GCase and DLB in humans. Titles and abstracts were the base of the initial screening. We evaluated the eligibility of selected articles after full text readings. Preclinical studies (cell lines or animal models) were excluded, as well as studies focusing only on PD; studies published in languages other than English, Reviews, Opinion papers and Duplicates were excluded. Data including study design, number of subjects, demographic data, clinical, genetic, biological, pathophysiological and neuropathological characteristics, main outcomes measures, main results and conclusions were extracted by 8 authors according to their field expertise (CP JH SG CH FM-L EA MF PM) using a standardized extraction form. The strength of clinical data were graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence.[13] The OCEBM framework levels range from 1–5, with 1 the highest level of evidence (Properly powered and conducted randomized clinical trial; systematic review with meta-analysis) and 5 the lowest level (expert opinion without explicit critical appraisal). Level 2 evidence is obtained from well-designed controlled trials without randomization or prospective comparative cohort trials. Level 3 corresponds to case-control studies or retrospective cohort studies, and level 4 refers to case-series. Studies that ranked level 5 on the OCEBM scale were excluded.

RESULTS

232 studies were screened and assessed for eligibility. After applying inclusion and exclusion criteria (**Supplementary Figure 1**), 29 clinical studies were selected for inclusion. We summarized clinical study findings and evidence levels in **Table 1**.

Clinical studies

Epidemiologic and cohort studies

Epidemiological studies have demonstrated that heterozygosity for common mutations in the GBA1 gene have been more frequent among patients with DLB than in the general population. As detailed in **table 1**, the

frequency of the most common mutations in GBA1 gene was highly variable, from 3% to 31% of DLB cases.[5,6,14–18] Furthermore, the strong association between GBA1 mutations and DLB (OR: 8.28) was higher than reported in PD (OR: 5.43) and in PD with dementia (OR: 6.48).[7,8] In addition to the two mutations most frequently associated with PD (N370S and L444P), the E326K variant is over-represented in DLB patients and is strongly associated with pure-DLB. In an Ashkenazi Jews cohorts of patients diagnosed with DLB, about 30% are carriers of mutations in the GBA1 gene.[15,22] Concerning the sex ratio in GBA1-associated DLB, several studies have observed a higher rate of men (from 65% to 90%) in all mutation carriers.[19]

Human neuropathology

Neuropathological studies suggest a strong association between GBA1 mutation and LB-type pathological changes. GBA1 mutation status was significantly associated with the presence of cortical LBs and GBA1 mutation carriers were significantly less likely to meet AD neuropathological criteria. In a retrospective cohort study of 213 autopsy-confirmed LB spectrum disorders patients, Irwin et al. 2017 reveal a decreasing frequency of heterozygous patients carrying the GBA E326K risk allele or GBA1 mutation with increasing levels of AD neuropathology.[23] Thus, GBA1 mutations may be associated with pathologically "purer" LB disorders, characterized by a more diffuse pattern of LB distribution involving the cerebral cortex, and less severe AD pathological findings.[14,24,25] In parallel, a few studies have shown decreased GCase protein and mRNA levels and reduced GCase enzyme activity in the brains of DLB with or without GBA1 mutations compared to controls.[26–28] However, population stratification based on GBA1 genotype demonstrated substantially lower GCase activity in carriers than in non-carrier, both in the study by Moors et al 2019 in DLB patients and in the study by Clark et al 2015 in patients with LB spectrum disorders.[28,29] In 2019, Gündner et al[30] demonstrated that in the substantia nigra, reduced GCase levels contribute to the increase in SNCA levels and to DLB disease manifestation partly by increasing its glycolipid substrate glucosylsphingosine. This result was concordant with a more pronounced alteration of lipid profiles in LB disease brains of GBA1 mutation carriers compared to non-carriers.[29] In 2021, Kurzawa-Akanbi et al[31] showed that extracellular vesicles purified from LB disorders *post-mortem* CSF and frontal cortex were heavily loaded with ceramides and neurodegeneration-linked proteins including SNCA and tau. However, GBA1 carriers did not show greater

sphingolipid levels than non-carriers. These findings indicate that abnormalities in ceramide metabolism are a feature of LB disorders, and that GBA1 modulates the risk of alpha-synucleinopathies, rather than induces it, and extracellular vesicles are likely involved in disease propagation.

Clinical characteristics

All clinical studies are summarized in **table 1**. To date, 7 studies assessed the clinical characteristics of patients with DLB and GBA1 mutations between 2003 and 2022. All those studies have described that GBA1 mutation carriers were younger at symptom onset with more frequent hallucinations, more pronounced parkinsonism and poorer cognition.[8,15,19,22,32–34]

Biological Biomarkers

Concerning biological biomarkers, several approaches have used either CSF or peripheral blood to assess GCase, SNCA or GBA1 transcript variants in patients with or without GBA1 mutations. The corresponding 4 studies are described in **table 1**.[27,34,35] Unfortunately, all these studies have included a small number of patients and have explored different biomarkers preventing comparability of the data. In 2019, Lerche et al[34] showed decreased CSF levels of total SNCA in DLB presenting a severe pathogenic GBA1 mutation compared to DLB patients with a mild mutation and non-carriers. In a neuropathological study, Perez-Roca et al[27] have shown that early-onset DLB patients had lowest levels of GBA1 transcript variants (GBAtv1) in blood. In 2022, Usenko et al[36] demonstrated pronounced alterations of lysosomal activities measured by liquid chromatography tandem-mass spectrometry in blood in patients with DLB. An on-going study (EGELY)[37] aims to determine if GCase activity is decreased in the blood of DLB patients to identify a subpopulation eligible for a therapeutic trial.

Treatment

So far, no curative or symptomatic treatments have been validated in DLB-GBA1 mutation carriers. Two on-going clinical trials are evaluating the safety and efficacy of Ambroxol in DLB, including genetic analysis of GBA1 gene. Both studies are presented in **table 1**.[38,39]

DISCUSSION

In this review, we have synthetized current clinical research evidence in GBA1-associated DLB. Clinical research confirmed the strong association between GBA1 mutations and DLB and suggests that GBA1 mutation carriers present a more severe phenotype across the spectrum of LB disorders, with an earlier age at symptom onset, more severe motor and cognitive dysfunction, more visual hallucinations and REM sleep disorders. Neuropathological studies show that GBA1 mutations are associated with pathologically "purer" LB disorders, characterized by a more diffuse pattern of LB distribution involving the cerebral cortex, and less severe AD pathological findings. Few studies have assessed potential biological biomarkers in DLB subjects with a GBA1 mutation. No therapeutics have been validated yet for GBA1-associated DLB and clinical trials assessing treatments that increase GCase activity are just starting in DLB patients.

Several epidemiologic studies have confirmed that GBA1 gene mutations were linked to an increased risk of DLB. However, the frequency of GBA1 mutations was highly variable, possibly due to various genetic methods from exploration of GBA1 mutations to full genotyping and to the exploration of different populations. Data are consistent in Ashkenazi Jews who seems at higher risk of GBA1 mutations and LB pathology. Larger studies from general population would be needed but the diagnostic difficulty and the lack of diagnostic accuracy in epidemiological cohorts preclude such studies for the time being. Such studies, in alive patients, could be done in more specific cohorts like ADNI,[40] EPAD,[41] BALTAZAR,[42] PPMI[43] and French MEMENTO Cohort.[44]

The results of all clinical and neuropathological studies are consistent and suggest a more severe phenotype and more and purer LB brain load in DLB patients carrying a GBA1 mutation. However, all studies have some limitations mainly the lack of longitudinal follow-up and all except one[23] explored small cohort size. Interestingly, even if the evidence base in DLB is still limited, results of all studies are concordant with the results of similar studies exploring GBA1 mutations in PD. These findings suggest that GBA1 mutations and

impaired GCase activity are aggravating factors for the pathophysiology and symptoms of alpha-synucleinopathies, particularly in psychiatric and cognitive clinical forms.

Similarly, neuropathological studies have demonstrated that GBA1 mutations seem to be an aggravating factor for decreased brain GCase protein levels and GCase enzyme activity. However, studies have also described that the levels of GCase protein and enzyme activity were reduced in DLB patient non-carriers of GBA1 mutations, confirming the hypothesis that there is a link between synucleinopathy and GCase but also that GBA1 mutations are probably not causative mutations but act as a confounding factor. Unfortunately, so far, there are few studies exploring biomarkers in alive patients in order to explore the link between GCase, brain and DLB. These kinds of studies would be required to validate GCase protein or activity level as a diagnosis and companion biomarker in case of treatment targeting GCase and efficient in DLB.

Lower GCase activity in CSF and brain samples of PD and DLB patients suggests a causal role of the lysosomal enzyme in these synucleinopathies. Preclinical research demonstrated that GBA1 mutants induce SNCA accumulations in a dose- and time-dependent manner.[45] Moreover, in synucleinopathy models, the activation of GCase, the use of glucosylceramide synthase inhibitors or acid ceramidase inhibitors all resulted in reduced accumulation of pathological SNCA.[46–48] *In vitro* and *in vivo* studies have reported that the pharmacological chaperone for GCase Ambroxol increases GCase enzyme activity and reduces SNCA levels. As in Gaucher Disease, other therapeutic approaches have to be considered including substrate reduction therapy with the glucosylceramide synthase inhibitor Venglustat and gene-replacement therapy PR001A to deliver a functional copy of the GBA1 gene to the brain. Venglustat development was stopped for PD in 2021 after the Phase 2 trial MOVES-PD missed its primary endpoint[49], but PR001A is currently tested in PD[50] and should be tried in DLB. The design of such studies would be easy in phase I and II but become much difficult in phase III. As GBA1 mutations appear as aggravating factors and as DLB clinical symptoms are variable according to patients, it will be difficult to define a precise and common primary clinical outcome for the efficacy of treatment. The design would probably require a homogenous population with the same phenotype profile in order to target specific symptoms.

Exploring the link between GBA1 mutations and DLB is a recent area of interest, with a limited number of preclinical and clinical studies in this field. Moreover, most clinical studies are case-control studies, with therefore a low quality of evidence. Future studies should precise the phenotype of GBA1-associated DLB, with longitudinal follow-up and neuropathological confirmation of the diagnosis. Further studies are needed to investigate the mechanisms by which GBA mutations may impact the natural history of DLB. This would help to confirm that GCase-based biological biomarkers (GCase activity or GBA1 transcript variants) could be valuable diagnostic biomarkers for DLB. Clinical trials are needed to best bring forward therapies to treat GBA1-associated DLB.

No clinical practice guidelines yet exist for GBA1 gene screening in patients meeting diagnostic criteria for DLB.[2] No clinical sign is specific of GBA1 mutations, but based on this review, an early symptom onset, a familial history of parkinsonism or GD, an initially severe motor and cognitive dysfunction or early psychosis should raise the possibility of a GBA1 mutation.

CONCLUSIONS

After the initial discovery of the role of GBA1 mutations and lysosomal impairment in the accumulation of SNCA and development of PD, evidence has emerged regarding the strong association between GBA1 mutations and DLB. Research work is still very recent in this field and contributes progressively to a better understanding of the pathogenesis of DLB. Hopefully, future studies will bring about improved phenotyping of GBA1-associated DLB, discovery of new biomarkers and effective therapeutic approaches.

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