Clinica Chimica Acta 495 (2019) 13–24

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Lysosomal enzyme activities as possible CSF biomarkers of synucleinopathies

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ARTICLE INFO

Keywords:
Lysosomal enzyme activity
Cerebrospinal fluid
β-glucocerebrosidase
Parkinson's disease
Synucleinopathies
GBA

ABSTRACT

Mutations on the *GBA* gene, encoding for the lysosomal enzyme β-glucocerebrosidase (GCase), have been identified as the most common genetic risk factor involved in the development of Parkinson's disease (PD) and dementia with Lewy bodies (DLB), indicating a direct contribution of this enzyme to the pathogenesis of synucleinopathies.

Decreased GCase activity has been observed repeatedly in brain tissues and biological fluids of both *GBA* mutation carrier and non-carrier PD and DLB patients, suggesting that lower GCase activity constitutes a typical feature of these disorders.

Additional genetic, pathological and biochemical data on other lysosomal enzymes (e.g., Acid sphingomyelinase, Cathepsin D, α-galactosidase A and β-hexosaminidase) have further strengthened the evidence of a link between lysosomal dysfunction and synucleinopathies.

A few studies have been performed for assessing the potential value of lysosomal enzyme activities in cerebrospinal fluid (CSF) as biomarkers for synucleinopathies. The reduction of GCase activity in the CSF of PD and DLB patients was validated in several of them, whereas the behaviour of other lysosomal enzyme activities was not consistently reliable among the studies. More in-depth investigations on larger cohorts, following stringent standard operating procedures should be committed to really understand the diagnostic utility of lysosomal enzymes as biomarkers for synucleinopathies. In this review, we reported the evidences of the association between the defective function of lysosomal proteins and the pathogenesis of synucleinopathies, and examined the role of lysosomal enzyme activities in CSF as reliable biomarkers for the diagnosis of PD and related neurodegenerative disorders.

1. Introduction

Parkinson's disease (PD), the most common neurodegenerative movement disorder, is pathologically characterized by the presence in selectively vulnerable brain regions of intracytoplasmic and axonal inclusions (i.e., Lewy bodies (LBs) and Lewy neurites), primarily consisting of aggregated α-synuclein (α-syn) [1].

Accumulation and formation of insoluble fibrillary α-syn is favoured by the impairment of the autophagy-lysosomal pathway (ALP), which represents one of the main routes implicated in the intracellular degradation of α-syn [2–7]. ALP plays a pivotal role in the cellular protein quality control system and its activity is relevant for maintaining the homeostasis of neurons. *In vitro* and *in vivo* studies have demonstrated that alterations in the autophagic flux upstream of the lysosomal degradative pathway can cause intracellular protein accumulation and lead to neurodegeneration [8–11]; several neurodegenerative disorders such as PD, Alzheimer's disease (AD), frontotemporal dementia (FTD) and Huntington's disease (HD) have been closely associated with

Abbreviations: AD, Alzheimer's disease; ALP, autophagy-lysosomal pathway; aSMAse, Acid sphyngomielinase; Aβ1-42, β-amyloid peptide 1-42; BH, brain homogenate; CatA, Cathepsin A; CatB, Cathepsin B; CatD, Cathepsin D; CatE, Cathepsin E; CatH, Cathepsin H; CatK, Cathepsin K; CatL, Cathepsin L; CMA, chaperone-mediated autophagy; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; DppI, Dipeptidyl peptidase 1; DppII, Dipeptidyl peptidase 2; FTD, frontotemporal dementia; GCase, β-glucocerebrosidase; GD, Gaucher disease; HD, Huntington's disease; iPSC, induced pluripotent stem cell; LB, Lewy body; LSDs, lysosomal storage disorders; MSA, multiple system atrophy; PD, Parkinson's disease; ROC, receiver operating characteristic; SapC, Saposin C; α-fuc, α-fucosidase; α-gal, α-galactosidase A; α-man, α-mannosidase; α-syn, α-synuclein; β-gal, β-galactosidase; β-hex, β-hexosaminidase; β-man, β-mannosidase

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https://doi.org/10.1016/j.cca.2019.03.1627
Received 12 November 2018; Received in revised form 19 March 2019; Accepted 23 March 2019
Available online 25 March 2019
0009-8981/

reduced lysosomal-mediated degradation [12]. The β-amyloid precursor protein (APP), for instance, is cleaved into smaller Aβ-peptides in the endosomal-lysosomal system. The impairment of lysosomal proteases activities influences the generation of Aβ-peptides, and leads to a pronounced build-up of potentially amyloidogenic protein fragments favouring the occurrence of AD pathology [13]. Furthermore, it is known that mutations in the gene encoding for presenilin 1 (PS1), a transmembrane protein essential for lysosomal acidification and proteolysis, causes an early-onset familial form of AD [14]. Dysfunction of ALP is also responsible for the onset of other neurodegenerative disorders, included FTD [15]. About the 5-25% of the familial FTD cases are caused by mutations in the gene encoding for progranulin (*GRN*). Progranulin is processed into granulin peptides, which seem to have an important role in regulation of lysosomal enzyme activities. It is worth to note that, while haploinsufficiency of *GNR* causes FTD, homozygous mutations in progranulin encoding gene cause neuronal ceroid lipofuscinosis (NCL), a form of lysosomal storage disorder. Interestingly, an overlapping of morphological, histological and biochemical traits between patients and animal models affected by FTD and NCL has been observed, further suggesting an alteration in lysosomal homeostasis. Another gene involved in the authopagic flux is the chromosome 9 open reading frame 72 gene (*C9orf72*) [16]. The abnormal expansion of a GGGGCC hexanucleotide repeat in a noncoding region of this gene is the most common genetic cause of familial and sporadic FTD. *C9orf72* appears to be a key autophagic regulator, indeed the presence of a pathological number of G4C2 repeats in C9orf72 is associated with impaired ALP.

Furthermore, mutations in other genes associated to FTD (i.e., *CHMP2B* and *VCP*), may contribute to the malfunctioning of ALP [17]. In HD, mutated huntingtin (mHTT) causes defective autophagy mediated degradation and accumulation of aggregated protein, which promote the increase of autophagosomes and the upregulation of autophagy. Interestingly, wild type HTT interacts with several regulators of autophagy and acts as a scaffold for autophagosome transport and biogenesis. It is worth to note that some neurodegenerative disorders, which share characteristics with HD, are caused by dysfunctional proteins involved in the autophagy and vesicular trafficking pathways [18].

A genetic link between the *GBA* gene, encoding for the lysosomal enzyme β-glucocerebrosidase (GCase), and both PD and dementia with Lewy bodies (DLB) has been observed in two large multicentre studies [19,20] and confirmed over time [21–23]. Mutations on the *GBA* gene are the most common genetic risk factors involved in the development of PD [19,24,25]; they also increase the risk of DLB by 9-fold, suggesting that genetic variants of the *GBA* gene contribute to the pathogenesis of synucleinopathies [20]. Several studies have demonstrated that genetic loss or pharmacological inhibition of GCase lead to accumulation and aggregation of α-syn in cells and animal models [26–34]. It is worth to note that the restoring of GCase activity in these models counteracts α-syn-induced toxicity [26,35,36]. A possible role of GCase in the spreading and propagation of synucleinopathy has also been suggested based on the observation of enhanced cell-to-cell transmission of α-syn aggregates in GCase depleted cells [37].

Notably, reduced GCase activity has been repeatedly documented in brain tissues and biological fluids of both *GBA* mutation carrier or non-carrier PD and DLB patients, suggesting that lower GCase activity is a typical feature occurring in these disorders [38–46].

Additional data from genetic, pathological and biochemical studies on other lysosomal enzymes such as Acid sphingomyelinase (aSMAse), Cathepsin D (CatD), α-galactosidase (α-gal A) and β-hexosaminidase (β-hex) have strengthened the evidence of a link between lysosomal dysfunction and synucleinopathies.

Variations of cerebrospinal fluid (CSF) lysosomal enzyme activities have been observed in patients affected by PD, DLB and AD [43,44,47–51]. Based on a recent study, lysosomal enzymes in CSF are of brain origin [52], thus it is reasonable to assume that the altered lysosomal enzyme activity reflects the pathological processes that take place in the brain, suggesting the utility of CSF lysosomal enzyme activities as diagnostic markers for neurodegenerative disorders.

This work summarizes the evidence of a link between the defective function of specific lysosomal proteins and synucleinopathies, focusing on the possible role of CSF lysosomal enzyme activities as biomarkers for PD and DLB.

2. Autophagy-lysosomal degradation pathway

Lysosomes are acidic organelles (pH 4.5-5) consisting of a single membrane layer, enriched with over 100 integral or membrane-associated proteins (i.e., receptors, transporters, anchoring proteins and membrane-bound enzymes), which encloses several hydrolytic enzymes (> 50). Lysosomes are directly involved in the digestion of damaged organelles and macromolecules in mammalian cells [53–55]. The degradation and recycling of cellular constituents occur in a multistep process that is carried out through the ALP pathway. The breakdown of a variety of complex molecules culminates with the release of their monomeric components via the concerted action of multiple soluble enzymes with different catalytic activities (i.e., nucleases, phosphatases, glycosidases, proteases, peptidases, lipases and sulfatases).

Lysosomal enzymes can degrade both material taken up from the extracellular milieu, as well as intracellular components that have been sequestered by autophagy [56]. Autophagy is a finely regulated process that contributes to reroute cytoplasmic components towards the lysosomal environment for degradation. The most well-established type of autophagy is known under the name of macroautophagy; this process involves the formation of double-membrane vesicles called autophagosomes that can be loaded, non-specifically, with bulky material destined to lysosomal degradation after fusing with the organelle [57]. The induction of autophagosomes formation can be triggered by different cellular stress conditions like aminoacid deprivation, endoplasmic reticulum (ER) stress derived from accumulated misfolded proteins or viral infections [58]. Dysfunctional cytosolic substrates could be also taken up directly by lysosomes through the formation of membrane invaginations and the release of the engulfed cargo in the lumen for digestion. This process, termed microautophagy, seems to participate in peculiar cell functions, such as presynaptic proteins turnover in neurons [59,60]. Another form of autophagy known as chaperone-mediated autophagy (CMA) allows the selective proteolysis of specific proteins bearing a KFERQ-like sequence. Tagged proteins are selectively recognized by the heat-shock cognate protein of 70 kDa (Hsc70) chaperone to build a complex that is specifically translocated to the lysosomes and internalized by the lysosomal associated membrane protein 2a (LAMP2a) receptor [61,62]. The high specificity of CMA ensures controlled degradation of regulatory proteins such as transcription factors or enzymes.

The blockade of the autophagic flux upstream of the autophagosomes building step, as well as the impairment of the lysosomal degradative function, can lead to the accumulation of dysfunctional proteins and organelles with relevant toxicity for the affected cells. Indeed, the catabolic function of lysosomes contributes to maintain the homeostasis of many cellular processes including the clearance of aggregated proteins (e.g., α-syn and β-amyloid1-42 peptide, Aβ1-42), which are implicated in the pathogenesis of neurodegenerative disorders like PD and AD, respectively [11,56,63,64].

Under physiological conditions, α-syn can be degraded by either CMA or by the ubiquitin-proteasomal systems [5]. Recently, CMA promotion has been shown to be protective from the development of PD by reducing the accumulation of misfolded α-syn in *Drosophila* neuronal cells [65] and the research for compounds exhibiting autophagy-enhancing properties to treat PD is currently under the attention of the drug discovery field [11]. Notably, in brains of PD patients impaired activity of GCase exacerbates α-syn accumulation with the formation of oligomeric toxic species, which results in an increased burden of

protein aggregates. These events lead to autophagic flux disturbances, to the irreversible inhibition of the cellular clearance systems and to the induction of an ER stress phenotype [26,66–68]. Thus, the discovery of agents that restore GCase activity currently represents an attractive strategy to obtain disease-modifying treatments for synucleinopathies.

3. Lysosomal storage disorders and synucleinopathies: evidence of a link

The lack of individual hydrolytic enzyme activities represents the main cause of lysosomal storage disorders (LSDs). LSDs are a heterogeneous group of disorders in which there is an abnormal accumulation of undegraded material inside the lysosomes, which impairs their function and can lead to cell death. To date, more than 70 LSDs were described accordingly to the type of impaired enzymatic activity and to the nature of the corresponding accumulated substrate [69,70]. Despite LSDs have detrimental effects on multiple organs and tissues, these disorders are commonly characterized by the presence of pathological marks in the central nervous system (CNS) [71]. The first evidence of a link between LSDs and neurodegenerative disorders comes from the observation of a Parkinsonian-like symptomatology in a small group of patients affected by Gaucher disease (GD) and their relatives [72–76]. GD is the most common LSD caused by mutations in the *GBA* gene, which result in deficient GCase activity.

The close interconnection between LSDs and PD has lately gathered attention because of the increasing number of reports about patients with LSDs showing Parkinsonian symptomatology (Table 1). The list of LSDs associated to PD includes Niemann-Pick diseases (type A/B and C, caused by mutations on *SMPD1* and *NPC1/2* genes, respectively), GM1 and GM2 gangliosidosis (resulting from deficient β-galactosidase (β-gal) and β-hex activity, respectively), neuronal ceroid lipofuscinoses (caused by mutations on *CLN1*, *2*, *3*, *4* and *10* genes), Fabry disease (caused by the mutations in the *GLA* gene, leading to α-gal A deficiency) and Kufor-Rakeb disease (due to mutations in the *PARK9* gene) [2,77–83].

In most of the described LSDs, neurological and motor impairment coexists with α-syn positive inclusions detected in brain tissue, underlying the importance of defective lysosomal enzyme activities in PD pathogenesis. For instance, in GD patients, alongside the accumulation of GCase substrate, the glucosylceramide, an immunohistochemical analysis of brain tissue showed the presence of LBs, mainly composed of aggregated α-syn [84]. Accumulated insoluble forms of α-syn were also found in cellular and animal models of GCase deficiency, including PD patient-isolated fibroblasts or iPSC-derived dopaminergic neurons, *GBA* mutants and PD mouse models, Drosophila models and zebrafish models [30,85]. All of these studies pointed out the reciprocal importance of GCase activity on α-syn levels and vice versa in PD. It is worth to note that the restoration of GCase activity by protein overexpression or by the treatment with small chaperone molecules in these models decreased the amount of α-syn aggregates [26,31,35,36,86]. A recent study has also shown that accumulation of glucosylceramide promoted α-syn oligomers formation and stability *in vitro* [87].

Mice lacking the lysosomal enzyme CatD also showed accumulation of endogenous α-syn in neurons due to the blockade of cellular ALP and proteasome pathways that are crucial for α-syn degradation [88]. Moreover, the presence of α-syn aggregates in β-hex deficient mice support the possible role of this enzyme in PD pathogenesis [89].

However, a few LSDs that display α-syn pathology have no classical PD symptomatology like in the case of mucopolysaccharidoses (namely Sanfilippo A and B diseases), multiple sulfatase deficiency (MSD), β-galactosialidosis (resulting from reduced activity of Cathepsin A (CatA)) and Krabbe disease (caused by mutations in the *GALC* gene, which impairs Galactocerebrosidase (GALCERase) activity). All these different clinical and neuropathological manifestations account for distinct pathogenic mechanisms and reflect the variety of manifestations observed among different types of synucleinopathies. While PD and multiple system atrophy (MSA) share a common background based on α-syn-related pathology, the role of lysosomal functionality seems to have a distinct contribution to their pathogenesis [90].

The importance of lysosomal activities in PD is highlighted by the recent observation that mutations on the Transmembrane protein 175 (*TMEM175*) gene, which encodes for a lysosomal membrane K^+ channel that regulates lysosomal pH, recapitulated common LSD phenotypes. Moreover, meta and conditional analyses of genome wide association studies (GWAs) conducted in PD patients associated this gene with the risk of PD development [91]. *TMEM175* mutations cause the alterations of multiple lysosomal enzyme activities, such as decreased GCase activity, impairment of autophagosomes clearance and mitochondrial functionality. Moreover, loss of the *TMEM175* gene increased the phosphorylation and aggregation of α-syn in rat primary neurons exposed to exogenous α-syn fibrils, indicating an enhanced susceptibility to PD development [92]. Additional studies on lysosomal activity-α-syn aggregation axis are required to reinforce the potential applicability of lysosomal enzyme activities assessment as an emerging tool for the diagnosis of synucleinopathies and to provide insights for establishing novel therapeutics able to modulate and to restore defective activities.

4. Genetic association between lysosomal enzymes and synucleinopathies

A large multicentre study on 5000 PD patients and healthy controls, showed that mutations on the *GBA* gene are the major genetic risk factor for PD [19]. Approximately 5–25% of PD patients are carriers of *GBA* mutations [25,85]; *GBA* mutation carriers have a 20-fold increased risk to develop PD as compared to non-carriers and the penetrance rate of PD by age 85 in these people is 10.9% [93].

The molecular mechanisms by which *GBA* mutations lead to an increased PD risk have not been fully elucidated. One of the main hypothesis is that a chronic loss of GCase activity, as well as a possible toxic gain-of-function of the mutated GCase might lead to lysosomal

Table 1
LSDs with Parkinsonism.

Lysosomal storage disease	Gene	Deficient enzyme/membrane protein	References
CLN10	*CTSD*	Cathepsin D (CatD; EC 3.4.23.5)	[88,130]
CLN2	*TPP1*	Tripeptidyl-peptidase 1 (TPP1; EC:3.4.14.9)	[131]
CLN3	*CLN3*	Battenin	[132,133]
CLN4	*DNAJC5*	DnaJ homolog subfamily C member 5	[134,135]
Fabry	*GLA*	α-galactosidase A (α-gal A; EC 3.2.1.22)	[136–138]
Gaucher	*GBA*	β-glucocerebrosidase (GCase; EC 3.2.1.45)	[19,20,25,30,31,77,78]
GM1 gangliosidosis	*GLP1*	β-galactosidase (β-gal; EC 3.2.1.23)	[51,80,139,140]
GM2 gangliosidosis (Tay-Sachs)	*HEXA*	β-hexosaminidase A (β-hex; EC 3.2.1.52)	[141,142]
Kufor-Rakeb	*ATP13A2* (*PARK9*)	Cation-transporting ATPase 13A2 (ATP13A2; EC 3.6.3.-)	[143–145]
Neuronal ceroid lipofuscinoses 1 (CLN1)	*PPT1*	Palmitoyl-protein thioesterase1 (PPT1; EC:3.1.2.22)	[146]
Niemann-Pick type A/B	*SMPD1*	Acid sphingomyelinase (aSMase; EC 3.1.4.12)	[113,147–149]
Niemann-Pick type C1/C2	*NPC1, NPC2*	Niemann-Pick C1/C2 protein	[79]

dysfunction and trigger the unfolded protein response and the ER-associated degradation pathway [85,94,95].

Although PD patients with *GBA* mutations seem clinically indistinguishable from sporadic PD, surprisingly, several studies have reported that the presence of *GBA* variants can lead to an earlier age of onset, higher risk of cognitive impairment and accelerated disease progression [96–100]. Furthermore, the presence of *GBA* mutations has been associated to rapid eye movement sleep behaviour disorder [101]. In longitudinal cohort studies, a faster worsening of motor symptoms has been observed in PD patients carrying *GBA* mutations [97,102]. Non-motor symptoms result more severe in *GBA* mutation carrier vs. non-carrier PD patients [85], and the risk of cognitive impairment is estimated to be higher for patients with *GBA* mutations; this trend has been particularly observed in subjects carrying mutations associated to the neuropathic form of GD [103,104].

DLB is also influenced by mutations on the *GBA* gene. *GBA* mutation carriers have 9-fold increased risk to develop DLB [20,105]. Significant worsening of cognitive performances were observed in DLB *GBA* mutation carriers among the Ashkenazi Jewish [106].

Along with PD and DLB, *GBA* variants are also associated to increased risk of developing MSA [107,108], further suggesting the connection between altered GCase function and defective α-syn clearance.

Other variants in lysosomal genes associated with PD susceptibility were proposed in recent studies such as *ASAH1* (Acid ceramidase), *CTSB* (Cathepsin B), *CTSD* (CatD), *GALC* (GALCERase), *SLC17A5* (Sialin), *SMPD1* (aSMase), *ATP6V0A1* (ATPase, H+ transporting, lysosomal V0 subunit A1) and *SCARB2* (Lysosomal integral membrane protein-2) [22,109]. It is interesting that, the genetic association between *GALC*, *SMPD1*, *ASAH1*, *SCARB2* and PD suggests a thorough involvement of sphingolipids degradation in disease pathogenesis, since the corresponding enzymatic activities take part to the same catabolic pathway of GCase. Particularly, the implication of *SMPD1* variants in PD is corroborated by several independent studies carried out among Ashkenazi Jewish and Chinese cohorts [110–115].

CTSD encodes for CatD, whereas *CTSB* for Cathepsin B (CatB), two proteases implicated in α-syn degradation [88,116,117]. It is worth noting that CatD is also responsible for the proteolytic cleavage of prosaposin, the precursor of GCase cofactor Saposin C (SapC) [118]. Thus, it might be possible that the presence of *CTSD* genetic variants alters CatD functionality, influencing not only α-syn catabolism, but also indirectly GCase activity via the impairment of SapC maturation.

An increasing number of mutations in lysosomal genes are currently associated to the enhanced risk of PD development and provide the main clues in defining the disease pathogenic mechanism by linking decreased lysosomal activity to the exaggerated accumulation of toxic species of α-syn.

5. Lysosomal enzyme activities in post mortem brain tissues

Although the growing list of genetic risk factors associated to the development of PD includes several genes encoding for lysosomal enzymes, only few studies have been performed concerning the reciprocal relationship between the impaired lysosomal functionality and the accumulation of α-syn (Table 2). The expression levels and the activities of some lysosomal enzymes, primarily the GCase, were investigated in brain homogenates (BH) derived from post mortem brains of PD patients or other related neurodegenerative disorders (i.e., DLB), with respect to healthy controls. GCase activity levels were found to be significantly reduced in several different brain regions such as the cerebellum, amygdala, putamen, and, in a major extent, in the substantia nigra of PD patients carrying GBA mutations, but not in the frontal cortex (not statistically significant but still decreasing) [38]. The enzymatic activity of GCase was also found to be reduced in the lysosomal-enriched protein fractions of early stage PD patients, more specifically in the anterior cingulated cortex and differently from the occipital cortex [39]. Notably, samples from PD patients without any known mutations in the GBA locus (sporadic PD) showed a significant reduction of GCase activity in the cerebellum, substantia nigra and caudate, when compared to controls, whereas no molecular explanations regarding this issue are currently available [38,40]. GCase activity was also confirmed to be reduced in DLB substantia nigra of a Dutch cohort [41], as previously suggested from a different cohort with similar results, even if not statistically significant [40]. No GCase activity alterations were found in frontal cortex, temporal cortex, hippocampus, cerebellum or putamen of PD or DLB patients [40,41,119]. At protein level, GCase has been shown to be reduced in cerebellum, substantia nigra, anterior cingulated cortex of both PD brains carrying GBA mutations and sporadic PD brains, but not in the occipital cortex [38,39]. Additionally, decreased GCase were observed in the putamen of the GBA carriers PD group alone [38].

Murphy and colleagues correlated the reduction of GCase protein in SDS-soluble fractions and activity to the increased amount of monomeric α-syn and reduced ceramide levels assessed in samples derived from early stage PD patients [39]. Diminished GCase activity and protein levels arise selectively in brain regions with increased levels of α-syn as documented by the fact that GCase and α-syn colocalize in LBs found in late stages of PD [120]. Variations in mRNA levels were observed only in two studies out of four, and only in the substantia nigra of both PD and DLB patients [40,41]. No variations were found in putamen, frontal cortex, anterior cingulated cortex, occipital cortex of GBA carriers PD or sporadic PD with respect to controls [38]. All these data support the possible pivotal role for the impaired GCase activity and α-syn accumulation in PD pathogenesis, which lead to the selective

Table 2
Recent studies and results in post mortem brain tissues.

Study	Cohort	Lysosomal enzyme	Activity	mRNA levels	Protein levels
Gegg *et al.*, 2012 [38]	BH, controls (n = 10)	GCase	↓[a]	n.s.	↓[a]
	PD + *GBA* (n = 14)	β-hex	n.s.	-	-
	sporadic PD (n = 14)	CatD	-	-	n.s.
Murphy *et al.*, 2014 [39]	BH, controls (n = 10)	GCase	↓[b]	n.s.	↓[b]
	PD (n = 19)	CatD	-	-	↑
		CatA	-	-	↑
		CatK	-	-	n.s.
Chiasserini *et al.*, 2015 [40]	BH, controls (n = 13)	GCase	↓[b]	↓[c]	-
	PD (n = 26)	β-hex	n.s.	-	-
	DLB (n = 16)	α-fuc	↓[b]	-	-
		β-man	n.s.	-	-
		α-man	↑[c]	-	-
		β-gal	n.s.	-	-
		CatE	n.s.	-	-
Moors *et al.*, 2018 [41]	BH, controls (n = 15)	GCase	↓[d]	↓[d]	-
	PD (late-stage, n = 15)	β-hex	n.s.	-	-
	DLB (n = 15)	CatD	↓[b]	n.s.	-
Nelson *et al.*, 2018 [119]	BH, controls (n = 12)	GCase	n.s.	-	-
	Stage IIa-IV	α-gal A	↓[b]	-	↓[b]
	PD (late-stage, n = 32)	CatD	↓[b]	-	-
		CatB	n.s.	-	-

Symbols indicate increased (↑), decreased (↓) or unaffected (not significant, n.s.) enzymatic activity, mRNA (qPCR) or protein levels (Western blotting).
BH – Brain homogenates; PD – Parkinson's disease; PD + *GBA* – *GBA* carriers PD patients; DLB – Dementia with Lewy bodies.
[a] $p < 0.01$, sporadic PD and PD + *GBA* vs. controls.
[b] $p < 0.05$, PD vs. controls.
[c] $p < 0.05$, DLB vs. controls.
[d] $p < 0.05$, PD and DLB vs. controls.

loss of dopaminergic neurons at the level of the substantia nigra.

Outside GCase, other peculiar alterations of lysosomal enzyme activities were found at the level of the frontal cortex like the decrease of α-fucosidase (α-fuc) activity and the increase of α-mannosidase (α-man) activity in PD or DLB samples, respectively [40]. In contrast, some of the activity assessed didn't show any significant modifications in the tested group, specifically the β-hex, β-mannosidase (β-man), β-gal, CatB and Cathepsin E (CatE) [38,40,41,119]. The stability of β-hex activity like that of other lysosomal enzymes reinforces the hypothesis of a selective dysfunction in PD pathogenesis, mainly focused on the sphingolipids degradative pathway, and excludes a pre-existing abnormal lysosomal biogenesis.

Recently, CatD, as well as, α-gal A activities were found to be significantly reduced in the temporal cortex of advanced PD patients [41,119]. Interestingly, negative correlations between the α-gal A activity and the 17 kDa phosphorylated α-syn (p129S-α-syn) and total α-syn monomer were described, similarly to that of GCase. Furthermore, both mRNA and protein (particularly the 46 kDa “active” isoform) levels for α-gal A were reduced in the temporal cortex of advanced PD patients. CatD gene and protein expression remained unchanged in the same group of study, accordingly to previously reported evidences in substantia nigra [38]. However, apparently contrasting results showing increased CatD protein levels, as well as CatA but not Cathepsin K (CatK), were described in BH of early-stage PD patients, suggesting a delayed involvement for these proteases in pathology evolution. To date, the only comparative study on samples representing different groups of neurodegenerative disorders such as AD, DLB, PD and HD was performed in 1995 by the assessment of the levels of activity of lysosomal proteases [121]. No significant differences emerged from the study for CatD, CatB, Cathepsin H (CatH), Cathepsin L (CatL) or Dipeptydil peptidase 1 (DppI) at the level of the frontal cortex of AD, DLB, PD samples. However, reduced DppII (Dipeptydil peptidase 2) activity was specifically found in DLB and PD groups. Moreover, increased CatD, CatH and DppII activities were observed in caudate of HD patients. A systematic analysis of the most recently associated lysosomal enzyme activities in a wider spectrum of neurodegenerative disorders could help in exploiting the distinctive molecular defects underlying different disease outcomes.

6. Lysosomal enzyme activity in CSF: studies in diagnostic cohorts

Along with the detection of the genetic and pathogenic link between some of the genes encoding for lysosomal enzymes and synucleinopathies, a few studies investigated the utility of CSF lysosomal enzyme activities for diagnosing PD and DLB by using well-established fluorogenic assays (Table 3) [122].

The most relevant impaired activity was GCase activity, which was found to be significantly reduced in different studies by comparing patients affected by PD with healthy or neurological controls (i.e., subjects without cognitive or motor impairments, but affected by other neurological conditions such as headache, peripheral neuropathies, epilepsy or postural instability) [43,44,51]. The lowered GCase activity was found in *GBA* mutation carriers PD and control subjects, compared to non-carriers [43,44]. Interestingly, the decrease of GCase activity in PD patients was consistent even after the exclusion of *GBA* mutation carriers from the analysis (-25% in non-carrier PD patients vs. non-carrier CTRL, $p < 0.001$) [44]. This finding demonstrates that the reduction of CSF GCase activity in PD is independent of the presence of mutations in the *GBA* gene. Reduced CSF GCase activity was also observed in DLB patients but not in patients affected by other forms of dementia (i.e., AD and FTD) or in neurological controls, indicating the selective involvement of this enzyme in disorders characterized by α-syn aggregation [123]. All these data are in agreement with the decrease of GCase activity repeatedly found in postmortem brain tissues [38,40,41,124,125] and dried blood spots [126] of both *GBA* mutation carriers and sporadic PD and DLB patients [40,41]. Only in one study GCase activity did not show any significant difference between PD patients and healthy controls [48].

The activities of other lysosomal enzymes were found to be altered in patients affected by synucleinopathies, however several of these findings have not been replicated. α-man and β-man activities were lower in the CSF of PD patients [51] with respect to neurological controls. A marked reduction of α-man activity was also found in DLB patients vs. neurological controls [123]. However, the activity of this enzyme was significantly lower even in patients affected by FTD and AD, indicating a poor discriminative power of α-man toward the synucleinopathies. CSF α-fuc [48] and CatD activities [44] were found significantly reduced in PD patients, whereas the activities of β-hex [43], β-gal and CatE [48] were significantly higher in PD with respect to healthy controls. It is worth to note, that without normalizing for the protein content, significantly higher β-hex activity was also observed by Parnetti *et al.* (unpublished data), confirming the trend toward the increase of β-hex activity in the CSF of PD [44].

Of interest, GCase and CatD activities were found significantly lower (-22% and -15%, respectively) in PD patients with higher Hoehn and Yahr score (H&Y ≥ 2) and in the same patients reduced GCase and β-hex activities were significantly associated with worse cognitive performance ($r = 0.26$, $p < 0.047$ and $r = 0.32$, $p < 0.004$, respectively) [44].

Despite the changes of CSF lysosomal enzymes activities in PD, the receiver operating characteristic (ROC) analysis showed that their discriminative power is quite poor when the enzymes activities are considered as single parameters. For instance, in one study GCase and β-hex activities were able to discriminate PD from neurological controls with low specificity (GCase: specificity 47.6%, sensitivity 85.7%; β-hex: specificity 52.6%, sensitivity 80.0%) [43], whereas better accuracy was obtained combining GCase activity with oligomeric/total α-syn ratio (o/t-α-syn) and age (specificity 71%; sensitivity 82%). In another study a suboptimal diagnostic accuracy for both GCase (specificity 77%; sensitivity 67%) and CatD activity (specificity 77%; sensitivity 61%) was obtained in distinguishing PD vs. healthy controls from BioFIND cohort [44]. The combination of GCase, CatD and β-hex activities showed a better diagnostic performance (specificity 85%; sensitivity 71%), which further improved including the levels of CSF α-syn and Aβ1-42 in the model (AUC = 0.83; specificity 75%; sensitivity 84%). Finally, a sensitivity and specificity of 63% in discriminate PD from healthy controls was obtained combining normalized β-gal and α-fuc activities [48].

All these data indicate that the combination of lysosomal enzyme activities in a wider panel of markers can improve the diagnostic accuracy in identifying PD patients versus controls. However, only one study evaluated the CSF lysosomal enzyme activities among different forms of dementia and no additional information are available on the behaviour of these enzymes in atypical parkinsonisms [123]. Thus, studies performed on larger cohorts, comparing patients affected by other neurodegenerative disorders, are required in order to confirm the diagnostic performance of lysosomal enzymes for the differential diagnosis.

7. Influence of pre-analytical factors on CSF lysosomal enzyme activity

The evidence that CSF GCase activity is reduced in PD patients with respect to both healthy and neurological controls, independently from the presence of *GBA* mutations, makes this enzyme a good biomarker candidate for PD diagnosis. However, GCase or more in general the CSF lysosomal enzyme activities, are highly influenced by pre-analytical factors. The high variability observed among the studies in terms of type, as well as in absolute values of enzyme activity, can be explained only in part by the heterogeneous characteristics of the selected cohorts. On the other hand, it is reasonable to assume that the conditions in which the samples are kept before freezing, the temperature and storage time, as well as the numbers of freeze/thaw cycles are the main

Table 3
Studies and results in CSF samples.

Study	Cohort	Lysosomal enzyme activities		Protein concentration	Diagnostic value, sensitivity – specificity (%)
Parnetti *et al.*, 2017 [44]	CSF (BioFIND cohort) controls (n = 61) PD (n = 79)	GCase β-Hex CatD	↓[a] n.s.[a] ↓[a]	↑	sens. 67–spec. 77, GCase sens. 61 – spec. 77, CatD[a] sens. 81 – spec. 42, t-α-syn sens. 63 – spec. 83, GCase[a] + β-hex[a] sens. 71 – spec. 85, GCase[a] + β-hex[a] + CatD[a] sens. 84 – spec. 75, GCase[a] + β-hex[a] + CatD[a] + t-α-syn + Aβ1-42
Parnetti *et al.*, 2014 [43]	CSF, OND (n = 45) PD (n = 71)	GCase β-Man β-Hex β-Gal	↓ n.s. ↑ n.s.	n.s.	sens. 47.6 – spec. 85.7, GCase sens. 52.6 – spec. 80.0, β-hex sens. 63.0 – spec. 75.7, t-α-syn sens. 41.6 – spec. 81.2, o-α-syn sens. 56.2 – spec. 85.7, o/t-a-syn ratio sens. 82 – spec. 71, GCase + o/t-α-syn ratio + age
van Dijk *et al.*, 2013 [48]	CSF, controls (n = 52) PD (n = 58)	GCase β-Man β-Hex β-Gal α-Fuc CatD CatE	n.s. n.s. n.s. ↑ ↓[a] n.s. ↑	↑	sens. 63 – spec. 63, β-gal[a] + α-fuc[a]
Parnetti *et al.*, 2009 [123]	CSF, controls (n = 23) DLB (n = 17) AD (n = 20) FTD (n = 20)	GCase α-Man β-Man β-Hex β-Gal	↓ (DLB) ↓ (DLB, AD, FTD) n.s. ↓ (DLB) ↓ (DLB)	-	-
Balducci *et al.*, 2007 [51]	CSF, controls (n = 20) PD (n = 12)	GCase α-Man β-Man β-Hex β-Gal	↓ ↓ ↓ n.s. n.s.	-	-

Symbols indicate increased (↑), decreased (↓) or unaffected (not significant, n.s.) enzymatic activity or total protein content in the selected CSF cohort vs the respective control group.
Cerebrospinal fluid; PD – Parkinson's disease; DLB – Dementia with Lewy bodies; AD – Alzheimer's disease; FTD – Frontotemporal dementia.
[a] Normalized activity against total protein content.

responsible for these variations.

In 1987 [127], for the first time, Goi *et al.* evaluated the stability of lysosomal enzyme activities, including GCase, in CSF. Activities were measured upon CSF storage in a temperature range from 37°C to -196°C (storage in liquid nitrogen). Several enzymes showed a rapid loss of activity within 15 days from CSF collection when stored at 37°C, 4°C and −80°C. The thermal instability described in this study led to consider lysosomal enzyme activities of poor clinical value for a long term storage. However, after the finding of the genetic link between lysosomal enzymes and synucleinopathies, the interest in evaluating the role of lysosomal enzymes as possible biomarkers, especially in response to the contrasting results obtained by different cohort studies, led to further investigations on these proteins. In 2014, Persichetti and coworkers systematically assessed the precision of the fluorogenic assays and the influence of the pre-storage and storage conditions, the stability in response to freeze/thaw cycles, the longitudinal variability of the enzyme activities up to 40 weeks and the effect of blood contamination for GCase, α-man, β-man, β-gal, β-hex, α-fuc, CatD and CatE (Table 4) [122]. Variability within- and in between run were both below 10%, minimally influencing the outcomes. Blood contamination did not significantly influence the enzyme activity up to 50000 erythrocytes/μl. Freezing conditions were evaluated by comparing three different procedures: flash freezing in liquid nitrogen, direct freezing at −80°C and direct freezing at −20°C. Among the enzyme activities assayed, only the α-man activity was significantly reduced when the samples were frozen at −20°C compared to the others methods. Pre-storage conditions differently affected each lysosomal enzyme: the most stable enzymes were β-hex, β-man and CatD, which showed no significant changes when stored at 4°C for 48 hours, in opposition to α-man, which resulted unstable at any evaluated time point. GCase activity decreased of 64% after 24 hours at 4°C and further decreased reaching 15% of residual activity after 48 hours. All enzymes were less stable when kept at room temperature; particularly, GCase and α-man showed a substantial decrease of activity already after 4 hours. As pre-storage conditions, the stability observed in response to freeze/thaw cycles also varied among the enzymes; GCase activity decreased nearly 15% and 45% after 2 and 5 cycles, respectively. Analysis of longitudinal variability up to 40 weeks showed that within the first week after storing, α-man activity decreased faster with respect to the other enzymes (similar data obtained by the same group led to the exclusion of this enzyme by a cohort study) [128]. β-hex and CatD had the higher degree of stability at −20°C up to 32 and 40 weeks, respectively. At

Table 4
Recommendations for pre-analytical issues associated to the assessment of the lysosomal enzymes activities in CSF.

Confounding factor	Recommendation	
Centrifugation	2000 ×*g* for 10 min, RT	
Temperature and time delay before freezing	4°C, < 1h	
Freeze-thaw cycles	Should be avoided	
Erythrocyte count	$< 50 * 10^3$/μl	
Freezing temperature	−80°C	
Length of storage	GCase	Up to 32 weeks
	CatD	
	CatE	
	α-man[a]	
	β-man	
	β-hex	
	α-fuc	Up to 16 weeks
	β-gal	Up to 4 weeks

RT: room temperature.
[a] α-man decreases of 20% of activity after 1 week at −80°C, after this time it remains stable.

−80°C, β-gal and α-fuc resulted the most unstable lysosomal enzymes, whereas β-man, CatD and CatE did not show any significant changes. GCase was stable for 32 weeks.

Each enzyme is affected differently by the pre-analytical confounding factors, for this reason the standardization of a protocol suitable for all lysosomal enzymes is difficult. However, for the proper assessment of lysosomal enzyme activities in CSF general guidelines should be followed: i) the CSF samples should be kept at 4°C immediately after the lumbar puncture (LP), centrifuged at 2000 × g for 10 min at room temperature, and stored at −80°C within 1 h of the collection; ii) β-man, CatD and CatE should be tested within 40 weeks from the LP, and GCase activity should be tested within 32 weeks; iii) the number of F/T cycles does not significantly affect CatD and CatE for up to 4 cycles, but they should be avoided for GCase and the other enzymes.

The operating procedures proposed above are in accordance, though more stringent in term of temperature and time delay before storage, and length of storage, to the standardized pre-analytical procedures used for the assessment of the classical CSF AD biomarkers analysed for diagnosis of dementia [129]. This is relevant if we look at the possibility of including lysosomal enzymes activities in a diagnostic panel of biomarkers.

8. Conclusions

The lack of biomarkers able to unequivocally identify patients affected by PD or DLB hampers the diagnosis at the earliest phases of these diseases, when treatments with forthcoming disease-modifying drugs may have the highest therapeutic impact. Thus, the identification of new molecules able to discriminate patients affected by synucleinopathies is mandatory. To date, the possible role as CSF biomarkers for synucleinopathies of several molecules (e.g., α-syn species, Aβ42, t-tau, p-tau, neurofilaments) has been widely investigated, whereas the highest accuracy in diagnosis has been obtained by combining different biomarkers reflecting the pathogenic mechanisms that take place during the course of the diseases. Encouraging results have been also obtained by cohort studies on lysosomal enzyme activities in CSF. Particularly, GCase activity has been found significantly reduced in PD and DLB patients with respect to both healthy and neurological controls, indicating the reliability of this data over different experiments. Moreover, in PD patients, the independence of the lower CSF GCase activity from *GBA* genotype, further suggests the more informative role carried out by GCase activity as a biomarker of synucleinopathies with respect to the genetic screening of *GBA*. Importantly, the combination of CSF lysosomal enzyme activities with α-syn species and Aβ42 significantly improved the accuracy in distinguishing PD vs. controls, indicating the essential contribution that these enzymes can provide in identifying PD patients [43,44]. The association between lower GCase activity and worse cognitive performance observed in PD patients as well as the reduction of GCase and CatD activity in the more advanced stages of the disease require to be analysed in-depth, in order to clarify the possibility of using GCase activity as a prognostic marker of cognitive impairment. For this purpose, longitudinal studies with CSF collection at different time points should be carried out.

In addition, the decrease in GCase activity observed in patients affected by DLB with respect to other forms of dementia, also encourages to investigate further the CSF lysosomal enzymes activities on larger cohorts including patients affected by different forms of dementia, to fully understand the real value of lysosomal enzymes for differential diagnosis and eventually as therapeutic targets. Similar analyses have to be committed also to evaluate the behaviour of these enzymes in atypical parkinsonisms like corticobasal degeneration and progressive supranuclear palsy.

The lack of standard operating procedures (SOPs) for CSF collection and sample handling caused high variability among the studies, sometimes also leading to contrasting results.

Differences in the stability of CSF lysosomal enzymes make difficult the comparison of activity values in longitudinal studies and their evaluation as progression markers. These limits prevent an unbiased evaluation of the diagnostic utility of CSF lysosomal enzyme activities. More investigations on larger and well-characterized cohorts, following stringent SOPs, are necessary to ensure a reliable assessment of the lysosomal enzyme activities in CSF and to understand thoroughly the value of these enzymes as biomarkers for synucleinopathies.

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