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Review

Diagnostic value of cerebro-spinal fluid biomarkers in dementia with lewy bodies

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ABSTRACT

Dementia with Lewy Bodies (DLB) is the second most common form of dementia after Alzheimer's disease (AD), accounting for 15% to 20% of neuropathologically defined cases. Two-thirds of the patients affected are not or misdiagnosed because of the clinical similarity of these two pathologies. In this review, we evaluate the discriminatory power of cerebrospinal fluid (CSF) biomarkers by focusing more specifically on differential diagnosis between DLB and AD. We focus on the AD biological biomarkers used in clinical routine as well as the biomarkers under study and more particularly the alpha-synuclein assay. Thus, among the AD biomarkers (t-Tau, phospho-Tau_{181}, Aβ42 and Aβ40) used routinely, t-Tau and phospho-Tau_{181} have shown excellent discrimination whatever the clinical stages severity. Aβ42 level is pathological in DLB patients at the demented stage, but is almost not impacted at the prodromal stage. Alpha-synuclein assay in the CSF has also an interest in the discrimination between DLB and AD but not in segregation between DLB and healthy elderly subjects. Thus, globally the biological diagnosis on CSF basis makes it possible, to separate the DLBs from the ADs. In addition, the development of biomarkers such as phospho-alpha-synuclein and oligomeric alpha-synuclein should help to reinforce this discrimination power.

1. Introduction

Dementia with Lewy Bodies (DLB) is the main cognitive neurodegenerative pathology of the elderly, after Alzheimer's disease (AD) [1]. DLB starts after 50 years old and represents 20% of demented patients [2]. The clinical diagnostic criteria for DLB were defined by McKeith and the DLB consortium [3,4]. The differential diagnosis is complex, the main confounding pathologies are AD, vascular dementia, Parkinson's disease dementia (PDD), progressive supranuclear palsy (PSP), multisystem atrophy (MSA), corticobasal degeneration (CBD) and prion diseases for brain diseases and psychosis, bipolarity for psychiatric diseases [2]. However, the most common differential diagnosis for the clinician remains with Alzheimer's disease (AD). Indeed, the usual symptoms of DLB are close to those of AD especially at the onset of the pathology: deficits in tests evaluating executive functions, visual memory, visuo-constructive and visuospatial abilities with weaknesses for episodic memory, short-term and working memory, verbal initiation, praxis, language, as well as social cognition [5,6]. In addition, DLB is also a pathology close to Parkinson's disease (PD), because of the presence of a parkinsonian syndrome (akinesia, rigidity more than resting tremor) often discreet at the beginning of the disease [7,8]. In addition, from a histopathological point of view, these patients share alpha-synuclein aggregates, commonly known as Lewy bodies [9]. These two pathologies, such as multiple system atrophy, are therefore part of synucleinopathies. The physiopathological difference that can be noted between DLB and PD is the aggregates localization. Lewy bodies are present in the substantia nigra in PD patients, whereas they are diffuse in the whole brain in DLB patients, particularly in the cortex. These latter have certain specificities such as illusions or visual hallucinations, attentional fluctuations, but also a particular sensitivity to neuroleptics [3] [8]. Despite the extremely high diagnostic specificity of these criteria (the specificity for a probable DLB - according to [7] - is 95.1% in the early stages and 88% in the late stages) [10], their sensitivity remains low (32%) in pure DLB [11]. Their sensitivity is even lower (12%) when DLB is associated with AD [11]. DLB and AD can often be associated, so Jellinger and Attems showed that among 1100 autopsied patients, 8.5% had pure DLB and 8.9% had AD with DLB [12]. This type of co-morbidity appears to be more common in elderly

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patients and the clinical aspect that emerges in these patients is more related to neurofibrillary pathology than to Lewy body pathology [13]. Thus, in these patients with AD/DLB comorbidity, DLB being masked, this pathology is more difficult to diagnose. In other words, DLB is still a largely underdiagnosed disease as more than two-thirds of DLB patients are undiagnosed or misdiagnosed. It should be noted that SPECT imaging (SPECT brain perfusion, [123I] FP-CIT SPECT) allows differential diagnosis at advanced stages (Burton et al., 2009) but does not always allow early diagnosis [14,15]. In brain MRI, there is at the prodromal stage greater hippocampal-parietal atrophy in AD. Thus in a differential diagnosis between DLB and AD, preserved hippocampal volumes are associated with an increased risk of probable DLB [16]. In addition, we participated in showing on a patient's cohort that there was an insular atrophy in the prodromal DLB [16–18]. Other potentially interesting tests to distinguish DLB from AD are DAT imaging, with a sensitivity of 78% and a specificity of 90% [19], but also MIBG scintigraphy. This scintigraphy quantifies postganglionic sympathetic cardiac innervation, which post-mortem studies show as reduced in DLB. Early studies suggesting a very high diagnostic accuracy were followed by others with lower sensitivity and specificity values, 69% and 87% respectively, but still useful in distinguishing probable DLB from probable AD, reaching 77% and 94% of cases with MMSE > 21 [20]. Polysomnographic demonstration of REM sleep without atonia is a predictor of Lewy-related pathology and has been incorporated in the revised DLB consensus criteria [4]. Nevertheless, it is essential to discover new biomarkers capable of discriminating DLB from AD to increase the differential diagnosis.

AD and DLB are both proteinopathies: AD is characterized by amyloïdopathy and tauopathy and DLB by synucleinopathy. Based on the pathophysiological characteristics of neurodegenerative diseases, it is possible to search for specific biomarkers in cerebrospinal fluid (CSF). Those of AD directly related to amyloidopathy and tauopathy (ie Aβ42, t-Tau, phospho-Tau_{181} and Aβ40) are commonly used in routine to diagnose it. Many publications have focused on the study of these biomarkers in dementias other than AD, and in particular in DLB patients. Thus, in this review, we will first evaluate the relevance of the biomarkers assay in the differential diagnosis between AD and DLB. We will see that these biomarkers have an interest in the discrimination of these 2 pathologies; however they are not specific enough for DLB. The improvement of the accuracy of the DLB diagnosis by the search for new biomarkers is of great interest. Because of its aggregation in the brain of DLB patients, alpha synuclein would appear to be a biomarker of interest in CSF, and it would theoretically discriminate AD from DLB patients. Other biomarkers, although not necessarily specific to DLB or AD, seem interesting for discriminating these two pathologies. We will discuss the relevance of these new biomarkers in a second part.

2. Methodology

The bibliographic search was conducted on Pubmed. Different keywords were typed for this search, such as “Cerobrospinal fluid AND Dementia with Lewy Bodies AND Alzheimer's disease” (110 results have been obtained and 38 results were used in this publication), “ Cerobrospinal fluid AND Alzheimer's biomarker AND Dementia with Lewy Bodies AND Alzheimer's disease “ (93 results have been obtained and 18 results were used in this publication), “ Cerobrospinal fluid AND differential diagnosis AND Dementia with Lewy Bodies AND Alzheimer's disease “ (55 results have been obtained and 20 results were used in this publication), “ Cerobrospinal fluid AND synuclein AND Dementia with Lewy Bodies “ » (47 results have been obtained and 18 results were used in this publication). Among the 94 useful publications highlighted in this bibliographic research there were redundancies, so 42 publications in total were actually used. The results of this research are between 1950 and June 1, 2018 (date of the last extraction on pubmed). In addition, our work on the DLB prodromal stage was useful, especially for Part 2.2). In total 39 publications were useful for our Part 2 and 23 publications were useful for our Part 3.

3. Relevance of Alzheimer biomarkers in the differential diagnosis between DLB and AD

3.1. Only the Aβ42 level is decreased in the CSF of DLB patients at the demented stage

Numerous studies have investigated the discrimination potential of Alzheimer's biomarkers (ie Aβ42, t-Tau, phospho-Tau_{181}, and to a lesser extent Aβ40) between AD and other related pathologies, such as DLB.

Phosphorylated Tau protein on threonine 181 (phospho-Tau_{181}) may be a useful biomarker for discriminating AD from DLB. Phospho-Tau_{181} is a rather specific marker of AD that alone can identify AD patients in a group of control patients and a group of patients with mild cognitive impairment (MCI) [21]. Actually, AD patients have higher phospho-Tau_{181} levels than DLB patients, making it possible to discriminate them with more or less sensitivity (75 to 94%) and more or less specificity (61 to 94%) according to studies [22–24]. Reviews on this subject have shown that phospho-Tau_{181} levels were generally unchanged in patients with dementia other than AD [25,26].

For **total-Tau (t-Tau)** concentrations in the DLB patients CSF, the majority of these studies showed a normal level or at least a lower level than in AD [23] [27–33]. However, some have dampened these results by indicating that despite significant differences between the two groups, the t-Tau levels in the CSF overlap between AD and DLB, [24] [34,35], or even that no significant difference is observable between the AD group and the DLB group [36] (autopsy verification). These results make the interpretation of this biomarker assay difficult in daily practice. However, overall, these studies indicate that this biomarker remains relatively good at discriminating AD from DLB since depending on the studies and cut-off used, the sensitivity varies from 72 to 79% and the specificity from 64 to 76%.

The majority of studies indicate, as in AD, an **Aβ1–42** level decrease in the DLB patients CSF compared to control patients and Aβ1–42 levels are not statistically different from those of AD patients [23] [33,34] [36]. To note, some studies have shown that the Aβ1–42 decrease in DLB patients was not as significant as in AD patients, such as Bibl et al. [37] who showed that this decrease measured by Aβ- SDS-PAGE / immunoblot was significant for patients with AD, but not for DLB patients. Thus, they showed that Aβ1–42 has good specificity (94%) but lost sensitivity (48%) when comparing AD patients to DLB patients. Similarly, Kasuga and colleagues [38] reported despite the Aβ42 decrease in DLB patients compared to patients with non-AD and non-DLB dementia that the Aβ42 level was higher, but not significantly, in patients with DLB than in patients with AD. Thus, it is possible that the Aβ1–42 level in the CSF of DLB patients at the demented stage is not as lowered as in AD patients.

Only a few studies have looked at **Aß40**, and overall this peptide appears to be decreasing in DLB patients compared to AD and control patients [30] [39,40]. However, other studies moderate these results as they have failed to demonstrate a significant Aβ40 decrease in DLB patients compared to controls [41,42]. Thus, while the majority of studies indicate no visible difference in Aβ42 levels in the CSF of AD and DLB patients, the Aβ42/Aβ40 ratio, thanks to the decrease of Aβ40 in DLB patients, improves the ability to discriminate AD patients from DLB patients, with a lower ratio in AD patients [39]. Note that this ratio also appears to be effective in discriminating AD from other dementias, with a sensitivity ranging from 73 to 94.7% and a specificity of 78 to 100% according to the studies [43–45].

3.2. The Aβ42 level is poorly impacted in the CSF of DLB patients at prodromal stages

The concept of mild cognitive impairment (MCI) is more recent in DLB than in AD [14]. Until recently, AD biomarkers levels had never

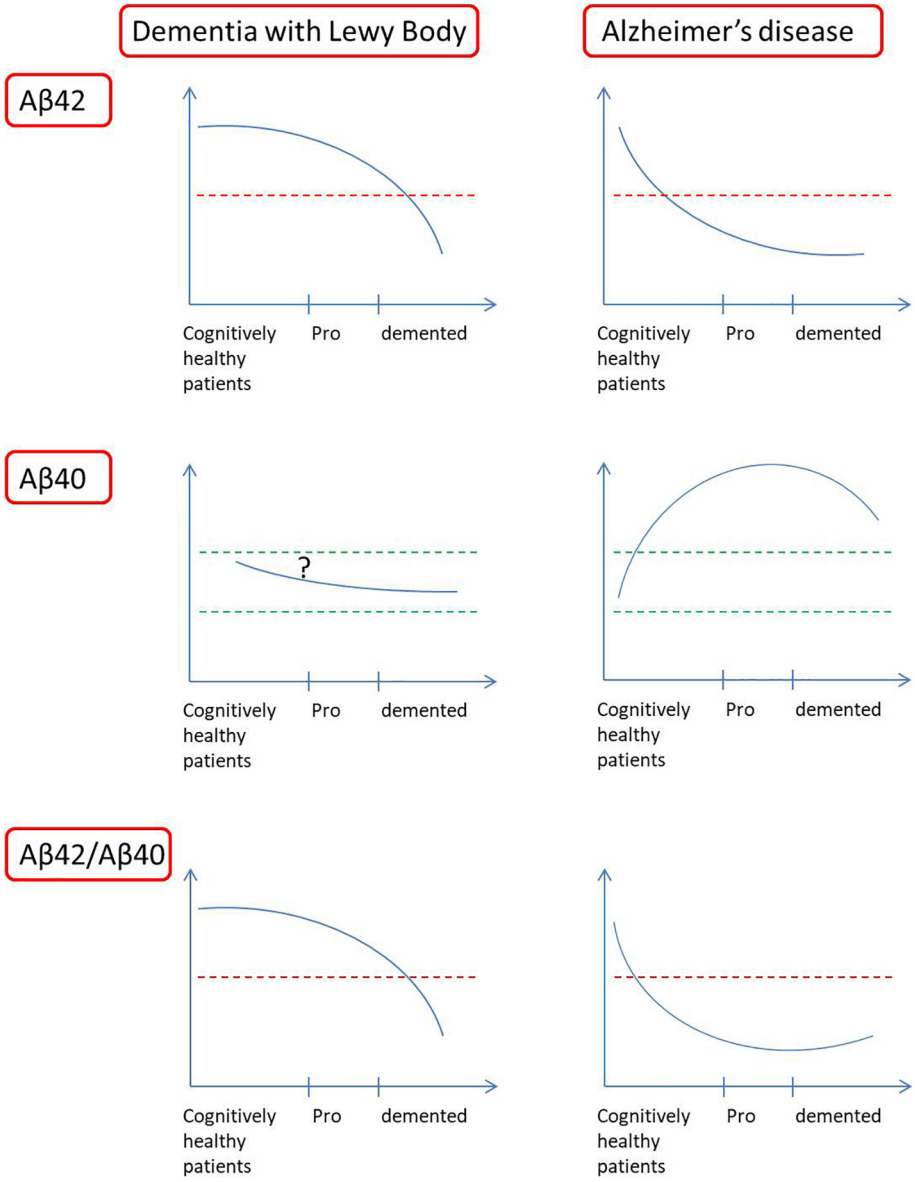

Fig. 1. Probable evolution of amyloid biomarkers (Aβ42 and Aβ40), during DLB and AD. The red dots represent the Aβ42 cut-off. The green dots represent the bounds of the Aβ40 normal value. Pro = prodromal stage of pathology. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

been studied at the MCI (prodromal) stages of DLB patients. Indeed, this group of patients was previously hardly diagnosed, but the clinical advances of recent years can better label these patients. Thus, prodromal DLB patients (DLBpro) may be defined as patients presenting the disease, but whose cognitive impairment is not sufficient to cause functional deficits in the instrumental activities of daily living and thus dementia [46]. Criteria for defining DLBpro have been proposed [8]: it can be defined as patients who meet the revised diagnostic criteria for DLB, but instead of dementia, meet the criteria for mild cognitive deficits (MCI) [46]. The cognitive profile of the DLBpro includes impaired tests evaluating visual memory, executive functions, visuo-contructive speed (TMTA) and abilities with weaknesses in verbal episodic memory, short-term memory, and working memory, verbal initiation, praxis, language, visuospatial abilities, and social cognition [5] [17]. Cerebral MRI studies in DLBpro patients have also shown focal atrophy of the insula [17] [47]. Thanks to these diagnostic advances, we have been able, in recent studies, to isolate these DLBpro patients and to analyze their T-Tau, phospho-Tau$_{181}$, Aβ42 and Aβ40 biomarkers levels [41,42]. These studies confirmed that t-Tau and phospho-Tau$_{181}$ biomarkers in DLB patients were not significantly changed whatever the stage. Moreover, a very slight Aβ42decrease in DLBpro patients compared to control patients was observed. This decrease was not as important as at demented stages (DLBd). These studies have demonstrated a significant Aβ42 decrease in the CSF between DLBpro patients and DLBd patients. These results are to be compared with those observed in other studies in which patients with dementia did not show an Aβ42 decrease as important in DLB as in AD patients [37,38]. Thus, unlike AD, where Aβ42 levels are at their lowest from the prodromal stages, in DLB patients the decrease occurs later between the MCI stage and the demented stage. An interesting study with autopsy verification showed that DLB patients with amyloid plaques had significantly lower Aβ42 concentrations in their CSF than DLB patients without amyloid plaques [48]. This suggests that DLB patients without a marked Aβ42 decrease do not have amyloid pathology. 73 to 87% of DLB patients will develop moderate to heavy amyloid plaques [48,49] explaining why Aβ42 levels in DLBd patients are, in the majority of studies, similar to those of ADd groups (eg [41,42]). These results suggest that DLBpro patients have few amyloid plaques. Thus, the later decrease of Aβ42

levels in the CSF of DLB patients compared to AD patients can be explained by the fact that amyloid deposits appear later, i.e. after aggregation of alpha-synuclein in DLB patients [49,50]. Overall, these studies indicate a strong link between synucleinopathy and amyloidopathy.

If the classical AD biomarkers evolution (t-Tau, phospho-Tau_{181}, Aβ42) is well described in AD and a consensus exist on their progression during the pathology, it is not the case for Aβ40. This is why in this part we will discuss the Aβ40 levels evolution, as well as the Aβ42/Aβ40 ratio, not only in DLB but also in AD. Regarding Aβ40, DLBpro showed no significant difference compared to control patients [41,42]. In contrast, we observed a significant Aβ40 increase in prodromal AD patients (ADpro) compared to control patients and DLB patients (pro and d). This Aβ40 increase in ADpro patients is a controversial point. Most studies have shown no change of the Aβ40 level in these patients [51,52]; one study showed an Aβ40 levels decrease in the CSF of these patients [53]. However, 3 more recent studies have shown a significant Aβ40 increase in AD patients, either in ADpro patients [54], or in a group with ADpro and ADd [43] or among patients with ADd [44]. Aβ40 is the amyloid peptide the most physiologically produced and could be the image of the overall production of amyloid peptides in an individual [55]. However, it has been shown that total Aβ amyloid peptides are clearly increased in ADpro patients [56], which is in line with this Aβ40 increase at the early stage of AD that we have demonstrated [41,42]. This Aβ40 level in AD patients then decreases significantly at the demented stages to return to almost the same level as the control patients [41,42] [54].

Thus, it seems likely that in AD and potentially in DLB, the Aβ40 level in an individual's CSF is not constant but evolves during the pathology.

Finally, the Aβ42/Aβ40 ratio is a very good tool for discriminating AD from DLB, essentially at the prodromal stage, the specificity ranging from 78 to 100% and the sensitivity ranging from 78 to 89% according to the studies [41,42] [51] [57].

Thus, the different AD biomarkers and particularly amyloid markers evolve during AD and DLB. In order to schematize these evolutions of the amyloid markers (Aβ42 and Aβ40), we have synthesized the literature, the figure below (Fig. 1) is representative of the probable evolution of these biomarkers in AD and DLB.

4. Alpha-synuclein assay in the differential diagnosis between DLB and AD

For the moment, only Alzheimer's biomarkers (Aβ42, t-Tau, phospho-Tau_{181} and Aβ40) are routinely available, but clinical research is very interested in alpha-synuclein. As in all neurodegenerative diseases (for review [58,59]), abnormal proteins aggregates were found in DLB; in this case, we found alpha-synuclein aggregates diffusely throughout the brain [9]. If alpha-synuclein aggregative phenomena appear in the brains of these patients, we can imagine that the protein concentration in the CSF is disrupted as are amyloid and t-Tau proteins in AD. Thus, studies on alpha-synuclein levels in the CSF have been developed in order to determine if this protein can represent a good biomarker for discriminating DLB from other neurodegenerative pathologies.

4.1. Differential diagnosis DLB-AD

Although there are some contradictions between the different publications concerning the alpha-synuclein assay in the CSF for the differential diagnosis purpose, a consensus seems to be established concerning this protein assay in the context of the differential diagnosis of synucleinopathies versus AD (for review [26] [60–62]).

Studies comparing the alpha-synuclein assay in DLB patients and AD patients are numerous and sometimes contradictory. Some publications have shown that the alpha-synuclein level in the CSF was higher in DLB patients compared to AD patients, the alpha-synuclein levels being otherwise identical between DLB groups, Parkinson's disease (PD), and controls [63,64]. Others have shown that there is no detectable change in alpha-synuclein levels in the CSF of DLB and AD patients [65–69]. However, the majority of studies indicate a lower alpha-synuclein level in DLB patients compared to AD patients and even more generally a lower level in synucleinopathies (PD, PD with dementia, DLB, multisystem atrophy MSA) compared to patients with AD [38] [70–76]. These results were confirmed on an autopsy series of patients [77]. These contradictory results can be explained by the fact that most studies use homemade kits, and their preparation can vary from one study to another. In particular, the antibodies used in the kits may be different, some kits measuring only the C– or N-terminal forms of the protein, or only some isoforms, make the assay of this marker heterogeneous between studies, and may also explain the performance differences of this biological marker. To be noted, the homemade kits do not always allow a good reproducibility depending on the batch, or may lack sensitivity, causing the non-detection of possible differences between groups. One study makes an interesting hypothesis concerning this results heterogeneity, showing by analyzing in a global way the alpha-synuclein level in the patients CSF, no significant difference between the DLB and AD patients could be detected, but by separating men and women, the authors showed a lower level of alpha-synuclein in DLB women compared to AD women, whereas no difference was detectable between men [78]. Thus, there may be a “gender effect” that may explain some of the observed differences in studies.

4.2. Differential diagnosis between DLB and healthy controls or other dementias

Thus, the majority of the studies observe lower levels of alpha-synuclein in the DLB patients CSF compared to AD patients, however, it is important to determine whether DLB patients are easily discriminated against healthy patients or those with another dementia. While low level of alpha-synuclein could be expected in DLB patients compared with control patients, very few studies have found this type of outcome [67] [70] [77]. The vast majority of studies indicate that there is no difference between alpha-synuclein levels in the CSF of DLB patients and control patients [63,64] [68–70] [72–76]. Again, Wennstrom and colleagues observed an alpha-synuclein decrease in DLB patients compared to controls, whereas no variation was observed in men [78]. However additional studies must be carried out to confirm it.

Most studies show some homogeneity among synucleinopathies: DLB patients, PD, PD dementia, and MSA have similar alpha-synuclein levels in CSF [63] [68–75] [77]. Only one study showed that alpha-synuclein levels were lower in DLB patients compared to PD patients [67]; anoher one with autopsy-controlled showed that AMS patients had a higher level of alpha-synuclein than in other synucleinopathies (PD, DLB) [79].

When synucleinopthies are compared with other dementias, again no variation is observed between groups (versus fronto-temporal dementia and vascular dementia, [66] versus PSP and cortico-basal degeneration [68] versus other dementias [38]), with the exception of Creutzfelt-Jakob disease where alpha-synuclein levels are above those observed in synucleinopathies [71].

In conclusion, it is generally observed that control patients, patients with synucleinopathies and even other dementias have rather homogeneous levels but are lower than those of AD patients, suggesting that the difference observed between DLB and AD patients is not due to a decrease in alpha-synuclein in DLB patients but rather to an increase of this protein in AD patients (see Table 1). This result is surprising because the physiopathological aspect of DLB, namely alpha-synuclein aggregates in the brain, is not highlighted in the CSF. Thus the alpha-synuclein assay may be relevant in the differential diagnosis between DLB and AD, but less in the case of DLB etiological diagnosis. Thus, it has been shown that the alpha-synuclein assay in CSF improves the

Table 1
summarizes the most probable changes of alpha-synuclein CSF from various demented diseases.

	Controls	AD	DLB	PD	MSA	CJD	Other demented pathologies (FTD, VD…)
Alpha-synuclein	N	N or ↑	N	N	N or ↑	N or ↑	N
References		[38] [70–77]	[63,64] [68–70] [72–76]	[63] [68–75] [77]	[63] [68–75] [77] [79]	[71]	[66] [68] [38]

AD: Alzheimer's disease.
CJD: Creutzfeldt-Jacob disease.
DLB: dementia with Lewy Bodies.
FTD: fronto-temporal dementia.
MSA: multiple sclerosis atrophy.
PD: Parkinson's disease.
VD: vascular dementia.

prognosis and biological diagnosis of Tau and Aβ in AD [80].

4.3. Other relevant biomarkers related to alpha-synuclein

The predominant alteration of alpha-synuclein in DLB is its phosphorylation on serine 129 (S129). Indeed, S129 is phosphorylated in > 90% of Lewy bodies, whereas physiologically this residue is phosphorylated in only 4% [81]. This phosphorylation may play a role in the alpha-synuclein aggregation, in the Lewy bodies formation and in neurotoxic processes [81]. S129-phosphorylated alpha-synuclein is therefore a good candidate for the differential diagnosis of DLB. Similarly, the alpha-synuclein oligomerized forms, leading to fibrilization and then to the formation of Lewy bodies and responsible for neurotoxicity in synucleinopathies may also be of interest in this diagnosis. So far, only one publication pays particular attention to these biomarkers, but no AD patients have been included in this study [79]. The authors included PD, PSP, CBD, MSA patients as well as control patients for whom lumbar puncture was performed at the time of the autopsy verification. Only MSA patients show an increase in the oligomeric forms of phospho-alpha-synuclein compared to other groups. Further studies must be performed to determine whether these biomarkers are of interest in the differential diagnosis of DLB.

4.4. Other potentially interesting biomarkers in the differential diagnosis between AD and DLB

Some biomarkers, despite a lack of direct specificity with either disease, are apparently able to differentiate AD from DLB. Currently three biomarkers stand out. These are YKL-40, Neurogranin, VILIP-1, which are related with neuroinflammation, synaptic dysfunction and neurodegeneration respectively.

YKL-40 also called chitinase-3-like protein 1 (CHI3L1) or cartilage glycoprotein-39 (HC gp-39) is a secreted glycoprotein with glycosyl hydrolases functions. In the brain YKL-40 is mainly expressed by astrocytes and plays a key role in inflammation especially in AD [82,83]. Despite neuroinflammatory events present in both AD and DLB, YKL-40 is increased in CSF of AD patients but not in DLB and CSF YKL-40 levels are significantly different between AD and DLB patients [84,85].

Neurogranin is calmodulin-binding postsynaptic protein playing an important role in memory by regulating synaptic plasticity and learning [86,87]. Thus the neurogranin release in the CSF is a reflection of synaptic dysfunction leading to neuron degeneration. Nevertheless synaptic dysfunction is a DLB feature [88], yet neurogranin levels in the CSF of AD patients are higher than in DLB patients [84].

Visinin like protein 1 (VILIP-1) belongs to the family of neuronal calcium sensors involved in calcium binding. A Ca^{2+} entry in cell lead to a reversibly VILIP-1 translocation to the membrane components of the cell. In this way VILIP-1 modulates signalling cascade in the neurons leading to the regulation of neuron ion channels, neuronal growth, survival, synaptic plasticity and activation of cyclic adenosine monophosphate (cAMP) and cyclic guanine monophosphate (cGMP) signalling pathways [89,90] A study has shown that the CSF VILIP-1 level had significantly increased in AD patients compared with both normal controls and DLB patients [76].

These three biomarkers appear promising in order to improve the differential diagnosis between AD and DLB. However these results will require further study.

5. Conclusion

The biomarkers used for the AD diagnosis (Aβ42, t-Tau, phospho-Tau_{181} and Aβ40) are the only ones available in hospital routine. However, their usefulness is undeniable in the differential diagnosis with DLB, the t-Tau and phospho-Tau_{181} values being the most discriminating biomarkers between these two pathologies. So an Aβ42 pathological level (with no other pathological biomarkers) is in favor of DLB. However, it should be noted that other demented pathologies may present an isolated decrease of Aβ42, such as for example in DLFT patients (for review [91]). Moreover, in DLB patients, an Aβ42 low value is in favor of a relatively advanced stage of the disease, since at the prodromal stage, the patients CSF has only little or no Aβ42 decrease. In addition to t-Tau and phospho-Tau_{181}, Aβ40 is relevant at the prodromal stage in this differential diagnosis, because Aβ40 levels are increased in AD patients. In addition, Aβ40 appears to be decreased in DLBd patients, so the discrimination is maintained in demented patients. Therefore, the ratio Aβ42 / Aβ40 is like t-Tau and phospho-Tau_{181} an excellent tool for discrimination whatever the stage.

Alzheimer's biomarkers are therefore useful in the discrimination between AD and DLB, however specific DLB markers are sorely lacking. Alpha-synuclein theoretically appears to be a good potential biomarker, due to its role in the DLB pathophysiology. However, published studies show that alpha-synuclein may actually be relevant in discriminating AD from DLB, but the changes do not come from DLB patients, but from AD patients. Currently no physiological explanation can explain these results in AD patients. Moreover, alpha-synuclein still does not clearly discriminate DLB from another demented pathology. Other biomarkers are under study. But whether the biomarkers are directly related to the alpha-synuclein such as S129 phosphorylation of alpha-synuclein, alpha-synuclein oligomers, or biomarkers without direct link with the aggregative processes of the pathology, such as YKL-40, Neurogranin, VILIP-1; these biomarkers suffer from a lack of hindsight to determine if they are actually relevant in the biological diagnosis of DLB. So far, currently no biomarker has shown a real specificity for DLB.

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