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Review Article

Biochemical Markers for Alzheimer's and Parkinson's Disease

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Abstract

Many biomarkers are currently being searched in neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. These diseases share some common pathophysiological mechanisms and the presence of protein aggregates. Measurements of those proteins -like tau, amyloid-beta peptide and α-synuclein-, as well other mediators of neurodegeneration in cerebrospinal fluid and peripheral fluids have been explored as biomarkers. Here we summarize some of the available data on biochemical markers for neurodegenerative diseases, considering advantages and drawbacks of each marker and method of analysis.

Keywords: Biomarkers, Alzheimer`s Disease, Parkinson`s Disease, Protein misfolding diseases

Abbreviations

AD: Alzheimer's Disease; PD: Parkinson's Disease; FTD: Frontotemporal Dementia; CBD: Corticobasal Degeneration; PSP: Progressive Supranuclear Palsy; MSA: Multiple System Atrophy; LBD: Lewy Body Dementia; PMDs: Protein Misfolding Diseases; α-syn: α-synuclein; CSF: Cerebrospinal Fluid; Aβ: Amyloid-beta Peptide; p-tau: Phosphorylated tau; AβPP: Aβ Precursor Protein; BBB: Blood-brain Barrier; miRNA: Micro RNA; mRNA: Messenger RNA; SPT: Serine Palmitoyltransferase; Sp 1: Specificity Protein 1; NINDCs: Non-inflammatory Neurological Disease Controls; EGF: Epidermal Growth Factor; CNS: Central Nervous System; TNF-α: Tumor Necrosis Factor-α; IL-1β: Interleukin-1β; IL-6: Interleukin-6; INF-γ: Interferon-γ; PGE2: Prostaglandin E2; TGFβ: Transforming Growth Factor β; IL-8: Interleukine 8

Background

As world population grows older, age related neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD) have become important public health concerns. Many other age-related conditions also share some combination of their most striking clinical features (i.e. dementia and Parkinsonism), so differentiation between some diagnoses may be very difficult in individual patients.

Among differential diagnoses for AD and PD we can mention many forms of frontotemporal dementia (FTD), corticobasal degeneration (CBD) progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and Lewy body dementia (LBD). All of the above also share the presence of protein aggregates on neuropathology, so they have been termed as protein misfolding diseases (PMDs) [1] and since tau or α-synuclein (α-syn) can be found frequently in protein aggregates, many of these diseases have been grouped as tauopathies i.e. AD, many forms of FTD, CBD and PSP [2-4] or as synucleinopathies i.e. PD, LBD and MSA [5]. Anyhow, is clear that multiple interactions exist between proteins in PMDs, so many proteins are affected in each PMD and conversely, most of the proteins described as responsible for PMDs show some degree of modification in each isolated PMD [5].

Many pathological processes appear to be related upstream in the process of protein aggregates generation, including misbalances in inflammatory responses, cell signaling and redox state. Even with all of our advances in the study of neurodegenerative processes and models of disease we have been unable to generate consensus on the true role of protein aggregates, so we still are not sure what is the true importance of protein deposition for PMDs and we don't know if there is a common pathway or generator of the pathological process (like neuroinflammation) in some or all of these diseases, and if there is a common pathway of neurodegenerative process, we don't fully understand what is the defining feature that initiates the deposition of one protein over the other and the neurodegenerative process of some neuronal populations over the next [6-9].

Since one of the main problems in the diagnosis of chronic neurodegenerative diseases is their late onset of symptoms many years after the disease has begun there is a big gap between initiation of pathologic processes and development of clinical symptoms. This is due to the brain extensive ability to compensate functions. This adaptive characteristic generates the problem that in most cases diagnosis is only possible late, when there is an advanced neurodegenerative process, so any present or future treatment will lose its effectiveness. Thereby, the development of suitable test able to identify diseases early, when symptoms are not so obvious has become an essential task for neurodegenerative diseases studies [10].

The lack of certainty on the pathophysiology of PMDs doesn't deny the fact that we have made many interesting discoveries on the biochemical and histopathological features that characterizes each form of PMD. Furthermore many groups have made efforts to follow up some of the changes in key biological markers a protein, cytokine, RNA or other and use them as biological marker for any disease they are interested on [7,9,11].

A biomarker can be defined as an indicator of the presence or extent of a disease in particular and is directly associated with clinical manifestations and prognosis [12,13]. They can be measured and evaluated as indicators of normal biological processes, pathogenic

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processes or pharmacological responses to therapeutic interventions. Currently, due to the limited availability and reliability of markers for PMDs scientists from several countries have focused on the discovery of these biomarkers [11].

The most important problem in the search for new biochemical markers of PMDs is the lack of standardization of sampling collection, handling and storage, as well as, the procedures that are performed for analysis -i.e. sample processing by western blot, ELISA, micro array, RT-q PCR or other. All of the above makes very difficult to achieve consistent results.

Since cerebrospinal fluid (CSF) is in close proximity with neural structures and is constantly exchanging different substances including all sorts of proteins -like the ones forming extracellular accumulates in PMDs, many research groups have focused on analyses of markers that may be present in CSF. Among those we can mention studies on levels of amyloid-beta peptide (Aβ), total tau protein, phosphorylated tau (p-tau) and α-syn for AD, PD and other PMDs [14]. Research has highlighted the increased hyperphosphorylated tau in the CSF of patients with AD and the close correlation between the levels of p-tau in CSF and cognitive impairment [14,15].

Aβ, tau and α-synas biomarkers for AD and PD

Aβ is one of the most prominent and well characterized aggregated proteins in neurodegenerative diseases, since it was initially reported by Glenner and Wong [16] it has become a cornerstone leading to a new front for research for the study of AD.

The amyloid precursor protein (AβPP) may be subject to the β-secretase pathway where two peptides may result, Aβ (1-40) and Aβ (1-42), however the Aβ (1-42) isoform has shown to be more toxic, it aggregates faster than Aβ40 and it is the main component of amyloid plaques in the extracellular space [17,18]. On the other hand, α-secretase acts in the non-amyloidogenic pathway, which doesn't lead to the Aβ formation [19]. Since Aβ deposition can be found in many neurodegenerative diseases, such as PD, AD [20], and LBD [21], it's been one of the most studied biomarker candidates.

Cerebrospinal fluid (CSF) is the main source for sampling Aβ and tau *in vivo* [4]. CSF is in intimate contact with nerve tissue, and there is an important exchange of substances with neural environment. For this reason, various groups have focused in modifications of various proteins and substances related to the pathogenesis of AD and PD [12,15,22,23] Considering a possible pathogenic role of Aβ, there have been lots of analyses of this protein. Measures of Aβ levels with immune assays in AD patients demonstrate a typical decrease in CSF's Aβ (1-42) levels, This sole analysis has a sensitivity of 78% and a specificity of 81-83% for the diagnosis of AD [4,24]. The reduction in Aβ has been attributed to aggregation and sequestration of Aβ (1-42) in brain senile plaques [25]. In AD there is also an increase in tau protein levels over time that has been attributed to neuronal degeneration and release of this intracellular protein [15]. As for other PMDs, studies in PD patients shows that tau levels seem unchanged and only Aβ (1-42) shows a decrease below base lines [20].

Previous studies demonstrate that even thought Aβ (1-42) measurements in CSF have sufficient accuracy over 85%- for discriminating between AD and control subjects [17,26]. The capacity of this biomarker for early differential diagnosis is still to low, because of a neuropathological overlap between AD and other PMDs like PD. Anyways Aβ (1-42) levels in CSF appear to be lower in AD patients than in PD [20,27].

Moreover, Siderowf *et al.* (2010), concluded that lower levels of CSF Aβ (1-42) were associated with cognitive decline in PD. Evaluating the relationship between Aβ (1-42), total tau and p-tau levels in CSF, and the change in cognition measured with Mattis Dementia Rating Scale (DRS-2), they showed that tau and p-tau didn't have any significant relationship with cognitive decline, however, when evaluating Aβ (1-42) they found that those with levels ≤ 192 pg/mL had a 6.1 points increase in annual decline compared to those above that level [25].

Low Aβ levels in CSF can predict the onset of cognitive decline in older women without dementia [28]. With respect to PD, studies by Bekris et al. 2015, found that Aβ levels are abnormal in the CSF of patients with PD. The objective of this exploratory study was to determine whether genetic variation within the AβPP is correlated with the levels of CSF Aβ (1-42) in PD. They studied single nucleotide polymorphisms (SNPs) from 19 regulatory regions of the nine genes (AβPP, *ADAM10, BACE1, BACE2, PSEN1, PSEN2, PEN2, NCSTN and APH1B*) involved in the cleavage of AβPP. They observed a significant correlation with Aβ (1-42) levels CSF in PD for two SNPs (AβPP rs466448 and *APH1B* rs2068143). In addition, the researchers suggest that SNP AβPP and SNP APH1B marginally associated with PD CSF Aβ (1-42) levels in non-carriers of *APOE*ε4 [29].

Studies focused on tau protein in CSF, showed that p-tau levels can be very useful, for example, p-tau phosphorylated at threonine 181 can discriminate between AD patients and control subjects and in patients with dementia with Lewy bodies. P-tau proved to be a better biomarker for AD compared to Aβ (1-42), and total tau [30]. Studies Maccioni *et al.* show increased hyperphosphorylated tau in AD patients, whereas only the subpopulation of patients with mild cognitive impairment (MCI) with greater cognitive impairment -which could be considered as preclinical AD showed abnormal increases in this tau variant [15]. During preclinical stages of AD, it is proposed that CSF Aβ levels may be a useful marker of asymptomatic cerebral amyloidosis, while evaluations of CSF tau and p-tau are best correlated with the later stages of synaptic dysfunction and early neurodegeneration [31,32].

Although CSF has proven to be a reliable source for biomarkers research, these kinds of analyses are not suitable for day-to-day diagnosis in clinical practice since lumbar puncture is considered too invasive as a routine diagnostic procedure. Thus, the search for less invasive and inexpensive diagnostic tools has driven researchers to explore peripheral biological fluids such as blood and saliva.

Plasma Aβ has been examined as a peripheral biomarker. However, the pool of circulating Aβ in plasma comes not only form brain tissue transported across the blood-brain barrier (BBB), but also from peripheral tissues and organs. This could be troublesome since Aβ measurements might not reflect the dynamics of senile plaque formation in the brain [18]. Platelets are an important peripheral reservoir for Aβ generation since they express AβPP. Furthermore platelets express the enzymatic mechanism necessary to process and release Aβ. Also, platelets can modify the soluble Aβ oligomers into Aβ (1-42). Gowert *et al.* (2014) have recently shown that Aβ improves

Table 1: Summary of biomarkers for Alzheimer's disease and Parkinson's disease.

Biomarker	Sample type	AD	PD	Reference
CSF amyloid-β	CSF	↓	↓	(4, 15, 24, 25, 29)
CSF tau	CSF	↑	↑	(4, 15, 31, 109)
Platelet AβPP (130/110kDa)	Blood	↓	NA	(33-36)
Platelet tau (HMW/LMW)	Blood	↑	NA	(4, 12, 22)
α-syn and DJ1	CSF	NA	α-syn ↓; DJ1 ↑	(38)
α-syn and DJ1	Saliva	NA	α-syn ↓; DJ1 ↑	(40)

Note: ↑: increase, ↓: decreases, NA: Not Applicable

platelets activation and generation of reactive species of oxygen, thus they concluded that platelets may have a role in cerebral amyloid angiopathy [33]. Modifications in platelets AβPP has been described in AD since an altered proportion of the different forms AβPP can be found in western blot with a decreased ratio high molecular weight (130kDa) to lower molecular weight (106 and 110kDa) forms of AβPP in AD patients compared to control groups [34,35]. However, it is important to consider that the changes in plasma concentration of Aβ (1-40) are nonspecific for AD and are closely related to age [36].

Tau has also been described in platelets. Studies by Farías *et al.* 2012 propose a new biomarker for AD, based on the detection of tau protein in platelets with specific antibodies. Some immunoreactive bands that have a higher molecular weight and appear to be oligomeric forms of the protein are increased in AD patients compared to healthy elderly subjects [12,22]. Later studies showed a close correlation between the degree of tau modification in platelets and the level of cognitive impairment measured by neuropsychological tests in subjects with AD and has been proposed as an AD biomarker with sensitivity of 75.7% and a specificity of 79.7% [4].

But plasma and platelets are not the only source for biomarkers in blood, Sotolongo-Grau et al. 2014, evaluated Aβ bounded in blood cells and searched a correlation between these Aβ levels and 45 regions of interest in the brain using magnetic resonance imaging. Surprisingly enough, the cell bounded Aβ (1-40) in blood was correlated with the volume of the left hippocampus while plasma Aβ showed no correlation with any of the studied brain regions [37].

Based on the research on Aβ and tau in CSF as AD biomarkers some groups have proposed a similar strategy for the search of PD biomarkers. Recent findings showed leading evidence for high specificity and sensitivity of α-syn and DJ-1 measurements in CSF in PD. Hong *et al.* (2010), evaluated 117 PD patients and 132 healthy controls. They found that levels of both proteins are lower in PD than in healthy controls [38]. Little is known about the exact biochemical role of DJ-1 in PD, however a study have shown evidence that DJ-1 eliminates the hydrogen peroxide, protecting the cells in oxidative stress. This is particularly interesting since, mutations on DJ-1 (L166P) are the cause of one familial form of PD (PARK7) [39].

Peripheral α-syn and DJ-1 have also been studied as peripheral PD biomarkers. It is described that the submandibular gland is intimately linked with synucleopathies since this gland is affected by histopathological changes typical of PD [21]. In this context, Devic et al. 2011 measured α-syn and DJ-1 in saliva, a really accessible and non-invasive fluid. For this study saliva samples were obtain from 24 PD patients and 25 healthy controls and. Even though results did not reach significance, they showed a trend towards decreased levels of α-syn levels and increased DJ-1 in PD patients. Additionally, they look for a correlation between these proteins and motor scores of the Unified Parkinson's disease Rating Scale (UPDRS), searching for a relation between these proteins and motor decline. Only α-syn levels showed a trend with UPDRS, but it didn't reach significance. Nonetheless, this study leads to an important hope for biomarkers on PD, as salivary fluid it's an ideal source for high-throughput assays [40].

MicroRNAs as biomarkers for PMDs

MicroRNAs (miRNA) are small RNA fragments from about 22 nucleotides length that regulates posttranscriptional processes by pairing with messenger RNA (mRNA).

miRNA expression varies depending on the physiological conditions of the cell, therefore that the study of circulating miRNA is a clue of what happens at the intracellular level in normal and pathological situations.

In their study, Geekiyanage and Chan (2011) showed that certain miRNAs related to modulation of ceramides levels-i.e. miR-137, -181c, -9, -29a/b-are down regulated in patients with AD, increasing the expression of the two subunits of serine palmitoyltransferase (SPT). mRNA levels did not differ in relation to control subjects, demonstrating that these are regulated post-transcriptionally, SPT1 by miR-137/-181c and SPT2 by -9, -29a/b, postulating these miRNAs as potential markers. A high level of ceramides in the brain has been associated with sporadic AD. In addition, it was demonstrated that down regulated miR-9 and miR-29 family members control BACE 1 in sporadic AD patients, inducing Aβ accumulation [41].

Sheinerman et al. (2012) took plasma from AD and MCI patients and control and identified several miRNA pairs (miR-128/miR-491-5p, miR-132/miR-491-5p, miR-323-3p/miR-491-5p, miR-134/miR-370, miR-323-3p/miR-370 and miR-382/miR-370). They conclude that although these miRNA pairs did not allow distinguishing between AD and MCI, they could be characteristics of neurodegenerative processes [42].

Leidinger et al. (2013) Identified 12 miRNAs in blood samples, that together, allowed to differentiate AD patients from control whit an accuracy of 93%, specificity of 95% and a sensitivity of 92%. These miRNAs can even differentiate between AD and other neurodegenerative diseases [43].

Transcription factor Sp1 (specificity protein 1) can control the expression of several protein associated with AD, including AβPP and tau. There is an inverse relationship between Sp1 mRNA and

miRNA 29b levels in peripheral blood mononuclear cells [44]. Sp1 and its regulatory hsa-miR-29b are deregulated in AD patients, may be causing abnormal expression of genes that are involved in illness.

A study observes the profile of circulating miRNA in serum and CSF of AD patients compared to non-inflammatory (NINDCs) and inflammatory neurological disease controls and patients with FTD. At the beginning, 84 miRNA were identified but it was demonstrated that only miR-125b levels are decreased in serum from patients with AD as compared with NINDC and distinguish between AD and NINDCs with an accuracy of 82% [45]. This result confirms a previous report for miR-125b [46], in which miR-125b was also postulated as a good candidate as a biomarker. miR-125b is brain-enriched and probably is involved in neurodegenerative processes [47].

In other study six miRNA that were increased in AD patients compared to control i.e. miR-98-5p, miR-885-5p, miR-483-3p, miR-342-3p, miR-191-5p, and miR-let-7d-5p- were identified. Within these six miRNA, it was found that miR-342-3p has the highest sensitivity and specificity and so, may serve as a novel, noninvasive biomarker for AD [48].

miRNAs have also been studied as a biomarker for PD; analysis from PD patient's blood reveled that three miRNA (miR-1, miR-22*, miR-29a) were down regulated in non-treated patients compared to control. A second group of three miRNA (miR-16-2*, miR-26-2*, miR-30a) presented a 50% increased in their relative expression between treated PD patients and control. In addition, miR-16-2*, miR-26-2* showed an increase in treated compared to non-treated patients [49].

Khoo *et al.* (2012) identified several circulating miRNA and their results were analyzed by two different strategies. k-TSP1 (miR1826/miR450b-3p), miR-626 and miR-505 attained the highest predictive power of 91% sensitivity, 100% specificity, 100% positive predicted value. However, in the replication set reached 88% negative predicted value [50].

In other work, plasma from PD patients and control was used and analyzed by microarray and qRT-PCR. A significant increased for miR-331-5 was found in PD patient's plasma versus control subjects. Moreover, bioinformatics analysis predicted that miR-331-5 could be involved in gene regulation implicated in PD. No other previously published miRNA was found [50].

Another report explored the alterations at the expression level of serum miRNAs in 10 idiopathic PD patients, 10 PD patients carrying LRRK2 G2019S mutation, and 10 controls by using RT-qPCR and miRNA arrays. Four statistically significant miRNAs were downregulated in either LRRK2 or idiopathic PD (miR-29a, miR-29c, miR-19a, and miR-19b). They validate the study, with another sample set, and confirmed the association of downregulated levels of miR-29c, miR-29a, and miR- 19b in idiopathic PD [51].

Inflammatory biomarkers

The inflammatory process is associated to the development of several neurodegenerative diseases. This process has cellular and molecular immune components such as microglial cells, cytokines and complement; they are main agents involved in the neuroinflammation, and act as inflammatory mediators. These proinflammatory mediators are either produced locally within the Central nervous system (CNS) or recruited from the peripheral circulatory system following disruption of the BBB. Based in this context, it is possible that the peripheral concentrations of inflammatory proteins may thus reflect changes in neuroinflammation in the CNS.

This in turn, leads to the activation of the glial cells, such as microglia and astrocytes. Neuroinflammatory mechanisms probably also contribute to the cascade of events leading to neuronal degeneration [52].

The identification and validation of molecules involved in this process could be a good strategy for finding new biomarkers. Usually, the inflammation does not trigger neurodegenerative process, but there is evidence that this constant inflammatory process leads to chronic activation of astrocytes and microglial cells contributing to disease progression [53].

Neuroinflammation characterized by microglial activation serves as an engine driving PD progression. In substantia nigra, many endogenous and exogenous factors activate microglia and produce neuroinflammatory factors [54], such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interferon-γ (INF-γ) and prostaglandin E2 (PGE2), which cause progressive neurodegeneration in dopaminergic neurons, and play an important role in the pathogenesis of PD [55,56]. After that, dead neurons release many substances to extracellular space including iron, aggregated α-synuclein and neuromelanin, inducing neuroinflammation, because all these components can trigger the activation of adjacent microglial cells [57], propagating progressive degeneration of dopaminergic neurons and deterioration of motor symptoms of PD [56]. In this way, the inflammation produced by microglial activation contributes to the cascade events leading to neuronal degeneration in PD [52].

Studies by Song group describes that the levels of hs-CRP (high-sensitivity C-reactive protein) and fibrinogen are significantly higher in groups of PD patients, more than those observed in a control patients. These findings are consistent with those reported previously and support the hypothesis that neuroinflammatory reactions are involved in the degenerative processes observed in PD [58,59]. Studies of biological fluids like serum or CSF also support a role for neuroinflammatory processes in Parkinson's disease. Specifically, an increase in TNFα, interleukin 1β, interleukin 6 and osteopontin (a member of the integrins family) has been reported in the CSF of patients with PD. The inflammatory changes are detectable during the course of the disease before the death of the patients and are associated with the progression of the disease [52].

In the other hand, studies by group of Lindqvist, in serum and CSF, show that PD patients had a significant increase in levels of IL-6 [60]. It is of some interest, therefore, that increased levels of IL-1b, IL-6 and TNFα have been found in the basal ganglia and CSF of PD patients [58], and the increase in TNFα, was particularly dramatic, being 366% in tissue and 432% in CSF [58].

Cognitive impairment is a very common non-motor symptom in PD patients, thus two major types of patients can be distinguished: the patients without cognitive impairment or dementia and PD patients with cognitive impairment or dementia. It may be very difficult to

diagnose these cases, therefore, identify a biomarker for severity of cognitive impairment becomes a necessity [56].

Also, PD patients with a high incidence of cognitive impairment (which mainly involves the cognitive domains of vocabulary memory, abstraction, visual-spatial and executive function and language), show elevated levels of IL-6 in CSF [56,60]. In this way it's possible to assume that IL-6 could be potential biomarkers for cognitive impairment in PD patients. Studies by Yu's group, show that demented PD patients have significantly higher level of C-reactive protein in CSF than non-demented PD and in the other hand, IL-6 level in CSF of cognitive impaired PD group is not only prominently enhanced comparing with the group of PD without cognitive impairment, but also has a strikingly negative correlation with MoCA score, indicating that IL-6 may be a potential neuroinflammatory biomarker for the development and severity of cognitive impairment in PD patients [56]. This may have important clinical utility for improving diagnostic accuracy, allowing better prognostication and earlier access to potential disease-modifying therapies [61].

In AD -the most common neurodegenerative disorder two characteristic lesions can be observed: extracellular amyloid aggregates containing Aβ and intracellular neurofibrillary tangles of hyperphosphorylated tau protein. The relationship between misfolding and aggregation of these two proteins and inflammation is based on the hypothesis that the complex nature of plaques and tangles stimulates a chronic inflammatory reaction to scavenge these wastes [62].

The presence of inflammatory process in AD brain has led to the discovery of increases in levels of various inflammatory mediators in cerebrospinal fluid (CSF). Further, abnormalities in immune-related molecules and functions have also been described in peripheral blood [63]. To date, studies of inflammatory biomarkers, in CSF or peripheral blood, of AD patients have also yielded inconclusive results.

It has been demonstrated that the lymphocyte biology is altered in AD. In blood samples from patients with AD, it's possible to observe alterations in intracellular calcium [64] and there is impaired release of IL-1β and IL-6 in response to stimulation with lipopolysaccharide (LPS). Furthermore there is a worsening of this process with disease progression [65]. In another study, LPS-stimulation resulted in exaggerated release of IL-1β, TNF-α, IL-6, and IL-10 [66].

Peskind measured levels of s100B, a protein secreted by astrocytes and directly linked to the inflammatory response, in the CSF of AD patients and healthy controls and found significantly elevated levels of s100B in CSF of mild or moderate AD patients, but declines to normal levels in more advanced stages of the disease [67]. S100B induces release of IL-6, which is one of components involved in the neuroinflammatory process [63]. IL-6 is a pleiotropic cytokine that mediates immune responses and inflammatory reactions affecting CNS cell growth and differentiation [68]. Also, IL-6 immunoreactivity is found within extracellular Aβ deposits [69]. Despite this, Mrak group have collected information about brain tissue levels of IL-6 that are not increased in AD, although increased levels of IL-6 mRNA have been reported in AD brain [63]. Cerebrospinal fluid IL-6 levels have revealed contradictory results unchanged [70,71] and increased [72,73]. One study found a correlation between CSF levels of IL-6 and tau levels in AD patients [63], but serum levels of IL-6 have reported controversial results, like increased [74] or normal [66].

Transforming growth factor β (TGFβ) is an important astrocytes derived cytokine that manifests both pro-inflammatory and anti-inflammatory properties. CSF levels of TGFβ were found to be increased in AD in one study [75] but decreased in other [76].

IL-1 is an immunoregulatory cytokine that is overexpressed within affected cerebral cortical regions of the AD brain [68]. Studies of IL-1 show opposite results, so it's like two groups found significant increases in AD patients [77] and others found no increase [78].

The pro-inflammatory cytokine TNFα has synergistic effects with IL-1 in inflammatory processes [63]. TNFα is an important mediator of systemic inflammation, activating the central innate immune response [79]. Studies in CSF of AD patients are conflicting since one group found elevated CSF TNFα levels [80] but a second group did not [81]. On the other hand, although most studies report an increase in the serum TNFα levels of patients suffering from neurodegeneration [82-84], one study reported TNFα attenuation in early-onset AD and late-onset AD patients [85].

Many studies have examined the correlation between TNFα levels and age. Production of TNFα is reported to be significantly higher in the elderly than in younger healthy volunteers, and results showed a significant positive correlation with age [74]. Another research by Angelopoulos et al. found a significant correlation between IL-6 and TNFα levels and age [86], and Holmes *et al.* 2011 demonstrated that elevated serum TNFα and IL-6 levels were associated with an approximately 2-fold increase in Neuropsychiatric Inventory scores and an increased frequency of adverse neuropsychiatric symptoms, independent of delirium [82]. Those studies suggested that acute and chronic systemic inflammation, which is associated with an increase in serum TNFα, is associated with an increased cognitive decline in AD [84].

Other component of the inflammatory process is interleukin 8 (IL-8), but the role of the IL-8 in AD progression is not well understood. IL-8 probably represents an additional recruitment mechanism for the migration of microglia to Aβ deposits, followed by a subsequent and persistent activation of microglial cells, favoring the neuroinflammatory context [87]. It is also known that IL-8 receptor has been localized in dystrophic neurites, suggesting that IL-8 mediates glial interactions with neurons and thereby contributes to neuronal damage [88]. Zhang *et al.* showed that levels of IL-8 in CSF of AD patients was significantly increased compared to healthy controls [89], whereas plasma levels of IL-8 in late-onset AD and vascular dementia did not differ from controls [90].

Currently, there is not a profile of inflammatory markers in CSF or plasma that may serve in the diagnosis of AD. In this context, Ray *et al.* performed combined multivariate analysis of plasma signaling and inflammatory proteins and found 18 plasma proteins that may identify AD patients and predict future AD with high accuracy in mild cognitive impairment (MCI) patients [91]. Another research group, Martins *et al.*, found that a set of 18 markers in blood had sensitivity and specificity of more than 80 % for distinguishing patients with Alzheimer's disease from healthy controls [92].

This is very relevant because all of these results could support the clinical diagnosis. Furthermore, it is important to consider that the incorporation of plasma biomarkers yielded high sensitivity with improved specificity, supporting their usefulness as a screening tool in the search of biological diagnosis of AD [93]. However, it will be very important for future clinical applications to find markers capable of differentiating AD from other dementias [62].

Others biomarkers for AD

Alteration in retina and visual defects are related to MCI and AD [94]. In addition, variations in visuospatial perception can be detected at first stage of AD [95].

Neurons need highly amounts of energy that is generated by mitochondria. Mitochondrial DNA is resistant to degradation because of its characteristic closed circular form, thus it can be present in CSF as a marker of neurodegeneration. It was demonstrated that low concentration mitochondrial DNA can be found in CSF of presymptomatic subjects who will develop AD, even before any change in Aβ or tau [96].

Ubiquitin is a protein involved in degradation of other proteins; it interacts with lysine residues and signals for degradations by proteases. In AD patients, PHF are ubiquitinated and ubiquitin conjugated protein can exist into the cell indefinitely [97]. It was demonstrated that increased levels of free and conjugated ubiquitin are found in CSF of patients with MCI progressing to AD [98]. Other group demonstrated that ubiquitin level were significantly higher in AD patients and found that a positive correlation between ubiquitin, tau and apolipoprotein Eε 4 genotype exists while there is a negative correlation with Aβ42 [99].

Plasma of AD patients has abnormal levels of phospholipids. Diminished level was observed also in people who will develop MCI and AD within 2-3 years -over 90% accuracy. That could be reflecting cell membrane integrity and consequently early neurodegeneration of preclinical AD [100].

Others biomarkers for PD

DJ-1 was a protein firstly identified in familial PD [101]. It is a multifunctional protein that plays an important role principally in oxidative stress. A study performed using whole blood from PD patients and healthy control found significant difference between DJ-1 isoforms levels, using 2D-electrophoresis, immunoblotting techniques and mass spectroscopy analysis. Although it was confirmed that not differences exists between total DJ-1 levels from PD patients and control, some isoforms in whole blood samples with 4-hydroxy-2-nonenal modifications were significantly increased and related to both PD diagnosis and PD severity [102].

Results from studies in CSF are not very consistent but one showed decreased level of DJ-1 in PD patients compared to control with a sensitivity of 90% and specificity of 70% [38].

Urate circulates at high concentrations in humans and also represents the principal end product of purine metabolism. It has antioxidant characteristics and thus protects against oxidative damage. Lower levels of uric acid could indicate increased risk and severity for motor symptoms of PD [103,104].

People with PD may develop cognitive impairment. Immunoassays from plasma samples, allowed identifying eleven proteins associated with cognitive performance, of which the most significant was epidermal growth factor (EGF). Suggesting that plasma EGF may be a biomarker for progression to cognitive impairment in PD [105].

Dihydroxyphenylacetic acid a neuronal metabolite of catecholamines metabolism- is diminished in patients with recent onset of Parkinsonism and may be used as a biomarker separating these patients from controls with 100% sensitivity and 89% specificity in [106].

Lower ApoA1 levels can be found in symptomatic PD patients and in asymptomatic individuals with physiological reductions in dopamine transporter density consistent with prodromal PD. It has been suggested that increasing plasma ApoA1 level in small amounts could reduce the risk of developing PD [107].

The Lewy body formation is due to the deficient protein degradation. Lysosomal hydrolases like GCase have been measured in CSF from PD patients and in other neurodegenerative disorders including LBD. The activity of GCase is reduced in PD and LBD patients in contrast to controls [108]. Therefore, the lysosomal dysfunction represents a good target to search for biomarkers.

Concluding remarks

AD and PD are currently recognized as the most common neurodegenerative diseases. Many efforts have been made to understand the pathophysiological mechanisms that underlie both diseases. Even though they appear as dissimilar conditions i.e. PD predominantly a motor disease and AD predominantly a cognitive disease- both are considered as PMDs and as such, share a lot of common mechanisms, including regulation of processes by miRNAs, generation of inflammatory signals, misfolding and aggregation of proteins. Our search for biomarkers must consider those markers that account for common neurodegenerative pathways from those that are specific for any PMD. Even if a perfect biomarker is not currently available we can advance in the definition of biomarkers profile that characterizes any neurodegenerative disease. Anyhow we must recognize that in order to validate any present or future biomarker is crucial to standardize the conditions for sample collection and processing. CSF is the most validated source for PMDs biomarkers' considering it reflects biochemical changes occurring in the CNS, but applicability of these biomarkers is limited because lumbar puncture is considered an invasive collection method [62]. On the other hand, blood samples are much easier to obtain, but concentrations of most potential neuronal biomarkers are several fold lower in blood than in CSF and there is a lot of "contamination" by plasma proteins that are not related to neuropathological processes. Given the multiplicity of pathophysiological processes implicated in PMDs, a combination of biomarkers related to different mechanisms might increase diagnostic accuracy and validity of any biomarker [62].

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References

1. Jellinger KA. Interaction between α-synuclein and other proteins in neurodegenerative disorders. ScientificWorldJournal. 2011; 11: 1893-1907.

2. Spillantini MG, Goedert M. Tau protein pathology in neurodegenerative diseases. Trends Neurosci. 1998; 21: 428-433.

3. Weaver CL, Espinoza M, Kress Y, Davies P. Conformational change as one of the earliest alterations of tau in Alzheimer's disease. Neurobiol Aging. 2000; 21: 719-727.

4. Guzmán-Martínez L, Farías GA, Maccioni RB. Emerging noninvasive biomarkers for early detection of Alzheimer's disease. Arch Med Res. 2012; 43: 663-666.

5. Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M. alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. Proc Natl Acad Sci U S A. 1998; 95: 6469-6473.

6. Morales I, Guzmán-Martínez L, Cerda-Troncoso C, Farías GA, Maccioni RB. Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches. Front Cell Neurosci. 2014; 8: 112.

7. Maccioni RB, Farías GA, Rojo LE, Jiménez JM. In Search of Therapeutic Solutions for Alzheimer's Disease. In: Mantamadiotis T, editor. Brain WTGW-DaDotH, editor. 2012. 125-150.

8. Jellinger KA. Interaction between pathogenic proteins in neurodegenerative disorders. J Cell Mol Med. 2012; 16: 1166-1183.

9. Alberio T, Fasano M. Proteomics in Parkinson's disease: An unbiased approach towards peripheral biomarkers and new therapies. J Biotechnol. 2010; 156: 325-337.

10. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7: 280-292.

11. Maccioni RB, Lavados M, Maccioni CB, Mendoza-Naranjo A. Biological markers of Alzheimer's disease and mild cognitive impairment. Curr Alzheimer Res. 2004; 1: 307-314.

12. Farías G, Pérez P, Slachevsky A, Maccioni RB. Platelet tau pattern correlates with cognitive status in Alzheimer's disease. J Alzheimers Dis. 2012; 31: 65-69.

13. McKhann GM. Changing concepts of Alzheimer disease. JAMA. 2011; 305: 2458-2459.

14. Lavados M, Guillón M, Mujica MC, Rojo LE, Fuentes P, Maccioni RB. Mild cognitive impairment and Alzheimer patients display different levels of redox-active CSF iron. J Alzheimers Dis. 2008; 13: 225-232.

15. Maccioni RB, Lavados M, Guillón M, Mujica C, Bosch R, Farías G, et al. Anomalously phosphorylated tau and Abeta fragments in the CSF correlates with cognitive impairment in MCI subjects. Neurobiol Aging. 2006; 27: 237-244.

16. Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. 1984. Biochem Biophys Res Commun. 2012; 425: 534-539.

17. Blennow K. CSF biomarkers for mild cognitive impairment. J Intern Med. 2004; 256: 224-234.

18. Schneider P, Hampel H, Buerger K. Biological marker candidates of Alzheimer's disease in blood, plasma, and serum. CNS Neurosci Ther. 2009; 15: 358-374.

19. Bohm C, Chen F, Sevalle J, Qamar S, Dodd R, Li Y, et al. Current and future implications of basic and translational research on amyloid-β peptide production and removal pathways. Mol Cell Neurosci. 2015; 66: 3-11.

20. Přikrylová Vranová H, Mareš J, Hluštík P, Nevrlý M, Stejskal D, Zapletalová J, et al. Tau protein and beta-amyloid(1-42) CSF levels in different phenotypes of Parkinson's disease. J Neural Transm. 2012; 119: 353-362.

21. Del Tredici K, Hawkes CH, Ghebremedhin E, Braak H. Lewy pathology in the submandibular gland of individuals with incidental Lewy body disease and sporadic Parkinson's disease. Acta Neuropathol. 2010; 119: 703-713.

22. Neumann K, Farías G, Slachevsky A, Perez P, Maccioni RB. Human platelets tau: a potential peripheral marker for Alzheimer's disease. J Alzheimers Dis. 2011; 25: 103-109.

23. Lin CH, Wu RM. Biomarkers of cognitive decline in Parkinson's disease. Parkinsonism Relat Disord. 2015; 21: 431-443.

24. Wiltfang J, Esselmann H, Bibl M, Hüll M, Hampel H, Kessler H, et al. Amyloid beta peptide ratio 42/40 but not A beta 42 correlates with phospho-Tau in patients with low- and high-CSF A beta 40 load. J Neurochem. 2007; 101: 1053-1059.

25. Siderowf A, Xie SX, Hurtig H, Weintraub D, Duda J, Chen-Plotkin A, et al. CSF amyloid {beta} 1-42 predicts cognitive decline in Parkinson disease. Neurology. 2010; 75: 1055-1061.

26. Tapiola T, Alafuzoff I, Herukka SK, Parkkinen L, Hartikainen P, Soininen H, et al. Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. Arch Neurol. 2009; 66: 382-389.

27. Schade S, Mollenhauer B. Biomarkers in biological fluids for dementia with Lewy bodies. Alzheimers Res Ther. 2014; 6: 72.

28. Gustafson DR, Skoog I, Rosengren L, Zetterberg H, Blennow K. Cerebrospinal fluid beta-amyloid 1-42 concentration may predict cognitive decline in older women. J Neurol Neurosurg Psychiatry. 2007; 78: 461-464.

29. Bekris LM, Tsuang DW, Peskind ER, Yu CE. Cerebrospinal fluid Aβ42 levels and APP processing pathway genes in Parkinson's disease. Mov Disord. 2015; 30: 936-944.

30. Vanderstichele H, De Vreese K, Blennow K, Andreasen N, Sindic C, Ivanoiu A, et al. Analytical performance and clinical utility of the INNOTEST PHOSPHO-TAU181P assay for discrimination between Alzheimer's disease and dementia with Lewy bodies. Clin Chem Lab Med. 2006; 44: 1472-1480.

31. Lavados M, Farías G, Rothhammer F, Guillon M, Mujica MC, Maccioni C, et al. ApoE alleles and tau markers in patients with different levels of cognitive impairment. Arch Med Res. 2005; 36: 474-479.

32. Cummings JL, Doody R, Clark C. Disease-modifying therapies for Alzheimer disease: challenges to early intervention. Neurology. 2007; 69: 1622-1634.

33. Gowert NS, Donner L, Chatterjee M, Eisele YS, Towhid ST, Münzer P, et al. Blood platelets in the progression of Alzheimer's disease. PLoS One. 2014; 9: e90523.

34. Padovani A, Borroni B, Colciaghi F, Pastorino L, Archetti S, Cottini E, et al. Platelet amyloid precursor protein forms in AD: a peripheral diagnostic tool and a pharmacological target. Mech Ageing Dev. 2001; 122: 1997-2004.

35. Borroni B, Colciaghi F, Caltagirone C, Rozzini L, Broglio L, Cattabeni F, et al. Platelet amyloid precursor protein abnormalities in mild cognitive impairment predict conversion to dementia of Alzheimer type: a 2-year follow-up study. Arch Neurol. 2003; 60: 1740-1744.

36. Luchsinger JA, Tang MX, Miller J, Green R, Mehta PD, Mayeux R. Relation of plasma homocysteine to plasma amyloid beta levels. Neurochem Res. 2007; 32: 775-781.

37. Sotolongo-Grau O, Pesini P, Valero S, Lafuente A, Buendía M, Pérez-Grijalba V, et al. Association between cell-bound blood amyloid-β(1-40) levels and hippocampus volume. Alzheimers Res Ther. 2014; 6: 56.

38. Hong Z, Shi M, Chung KA, Quinn JF, Peskind ER, Galasko D, et al. DJ-1 and alpha-synuclein in human cerebrospinal fluid as biomarkers of Parkinson's disease. Brain. 2010; 133: 713-726.

39. Taira T, Saito Y, Niki T, Iguchi-Ariga SM, Takahashi K, Ariga H, et al. DJ-1 has a role in antioxidative stress to prevent cell death. EMBO Rep. 2004; 5: 213-218.

40. Devic I, Hwang H, Edgar JS, Izutsu K, Presland R, Pan C. Salivary α-synuclein and DJ-1: potential biomarkers for Parkinson's disease. Brain. 2011; 134: e178.

41. Hébert SS, Horré K, Nicolaï L, Papadopoulou AS, Mandemakers W, Silahtaroglu AN, et al. Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/beta-secretase expression. Proc Natl Acad Sci U S A. 2008; 105: 6415-6420.

42. Sheinerman KS, Tsivinsky VG, Crawford F, Mullan MJ, Abdullah L, Umansky SR. Plasma microRNA biomarkers for detection of mild cognitive impairment. Aging (Albany NY). 2012; 4: 590-605.

43. Leidinger P, Backes C, Deutscher S, Schmitt K, Mueller SC, Frese K, et al. A blood based 12-miRNA signature of Alzheimer disease patients. Genome Biol. 2013; 14: R78.

44. Villa C, Ridolfi E, Fenoglio C, Ghezzi L, Vimercati R, Clerici F, et al. Expression of the transcription factor Sp1 and its regulatory hsa-miR-29b in peripheral blood mononuclear cells from patients with Alzheimer's disease. J Alzheimers Dis. 2013; 35: 487-494.

45. Galimberti D, Villa C, Fenoglio C, Serpente M, Ghezzi L, Cioffi SM, et al. Circulating miRNAs as potential biomarkers in Alzheimer's disease. J Alzheimers Dis. 2014; 42: 1261-1267.

46. Tan L, Yu JT, Liu QY, Tan MS, Zhang W, Hu N, et al. Circulating miR-125b as a biomarker of Alzheimer's disease. J Neurol Sci. 2014; 336: 52-56.

47. Sethi P, Lukiw WJ. Micro-RNA abundance and stability in human brain: specific alterations in Alzheimer's disease temporal lobe neocortex. Neurosci Lett. 2009; 459: 100-104.

48. Tan L, Yu JT, Tan MS, Liu QY, Wang HF, Zhang W, et al. Genome-wide serum microRNA expression profiling identifies serum biomarkers for Alzheimer's disease. J Alzheimers Dis. 2014; 40: 1017-1027.

49. Margis R, Margis R, Rieder CR. Identification of blood microRNAs associated to ParkinsonÄs disease. J Biotechnol. 2011; 152: 96-101.

50. Khoo SK, Petillo D, Kang UJ, Resau JH, Berryhill B, Linder J, et al. Plasma-based circulating MicroRNA biomarkers for Parkinson's disease. J Parkinsons Dis. 2012; 2: 321-331.

51. Botta-Orfila T, Morató X, Compta Y, Lozano JJ, Falgàs N, Valldeoriola F, et al. Identification of blood serum micro-RNAs associated with idiopathic and LRRK2 Parkinson's disease. J Neurosci Res. 2014; 92: 1071-1077.

52. Hirsch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol. 2009; 8: 382-397.

53. Meraz-Ríos MA, Toral-Rios D, Franco-Bocanegra D, Villeda-Hernández J, Campos-Peña V. Inflammatory process in Alzheimer's Disease. Front Integr Neurosci. 2013; 7: 59.

54. Block ML, Hong JS. Microglia and inflammation-mediated neurodegeneration: multiple triggers with a common mechanism. Prog Neurobiol. 2005; 76: 77-98.

55. Çomoğlu SS, Güven H, Acar M, Öztürk G, Koçer B. Tear levels of tumor necrosis factor-alpha in patients with Parkinson's disease. Neurosci Lett. 2013; 553: 63-67.

56. Yu SY, Zuo LJ, Wang F, Chen ZJ, Hu Y, Wang YJ, et al. Potential biomarkers relating pathological proteins, neuroinflammatory factors and free radicals in PD patients with cognitive impairment: a cross-sectional study. BMC Neurol. 2014; 14: 113.

57. Zhang W, Phillips K, Wielgus AR, Liu J, Albertini A, Zucca FA, et al. Neuromelanin activates microglia and induces degeneration of dopaminergic neurons: implications for progression of Parkinson's disease. Neurotox Res. 2011; 19: 63-72.

58. McGeer PL, McGeer EG. Inflammation and neurodegeneration in Parkinson's disease. Parkinsonism Relat Disord. 2004; 10 Suppl 1: S3-7.

59. Song IU, Kim YD, Cho HJ, Chung SW. Is neuroinflammation involved in the development of dementia in patients with Parkinson's disease? Intern Med. 2013; 52: 1787-1792.

60. Lindqvist D, Kaufman E, Brundin L, Hall S, Surova Y, Hansson O. Non-motor symptoms in patients with Parkinson's disease - correlations with inflammatory cytokines in serum. PLoS One. 2012; 7: e47387.

61. Magdalinou NK, Paterson RW, Schott JM, Fox NC, Mummery C, Blennow K, et al. A panel of nine cerebrospinal fluid biomarkers may identify patients with atypical parkinsonian syndromes. J Neurol Neurosurg Psychiatry. 2015.

62. Nuzzo D, Picone P, Caruana L, Vasto S, Barera A, Caruso C, et al. Inflammatory mediators as biomarkers in brain disorders. Inflammation. 2014; 37: 639-648.

63. Mrak RE, Griffin WS. Potential inflammatory biomarkers in Alzheimer's disease. J Alzheimers Dis. 2005; 8: 369-375.

64. Adunsky A, Baram D, Hershkowitz M, Mekori YA. Increased cytosolic free calcium in lymphocytes of Alzheimer patients. J Neuroimmunol. 1991; 33: 167-172.

65. Sala G, Galimberti G, Canevari C, Raggi ME, Isella V, Facheris M, et al. Peripheral cytokine release in Alzheimer patients: correlation with disease severity. Neurobiol Aging. 2003; 24: 909-914.

66. Lombardi VR, Garcia M, Rey L, Cacabelos R. Characterization of cytokine production, screening of lymphocyte subset patterns and in vitro apoptosis in healthy and Alzheimer's Disease (AD) individuals. J Neuroimmunol. 1999; 97: 163-171.

67. Peskind ER, Griffin WS, Akama KT, Raskind MA, Van Eldik LJ. Cerebrospinal fluid S100B is elevated in the earlier stages of Alzheimer's disease. Neurochem Int. 2001; 39: 409-413.

68. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, et al. Inflammation and Alzheimer's disease. Neurobiol Aging. 2000; 21: 383-421.

69. Bauer J, Konig G, Strauss S, Jonas U, Ganter U, Weidemann A, et al. In-vitro matured human macrophages express Alzheimer's beta A4-amyloid precursor protein indicating synthesis in microglial cells. FEBS Lett. 1991; 282: 335-340.

70. Hampel H, Schoen D, Schwarz MJ, Kötter HU, Schneider C, Sunderland T, et al. Interleukin-6 is not altered in cerebrospinal fluid of first-degree relatives and patients with Alzheimer's disease. Neurosci Lett. 1997; 228: 143-146.

71. März P, Heese K, Hock C, Golombowski S, Müller-Spahn F, Rose-John S, et al. Interleukin-6 (IL-6) and soluble forms of IL-6 receptors are not altered in cerebrospinal fluid of Alzheimer's disease patients. Neurosci Lett. 1997; 239: 29-32.

72. Wada-Isoe K, Wakutani Y, Urakami K, Nakashima K. Elevated interleukin-6 levels in cerebrospinal fluid of vascular dementia patients. Acta Neurol Scand. 2004; 110: 124-127.

73. Blum-Degen D, Müller T, Kuhn W, Gerlach M, Przuntek H, Riederer P. Interleukin-1 beta and interleukin-6 are elevated in the cerebrospinal fluid of Alzheimer's and de novo Parkinson's disease patients. Neurosci Lett. 1995; 202: 17-20.

74. Maes M, DeVos N, Wauters A, Demedts P, Maurits VW, Neels H, et al. Inflammatory markers in younger vs elderly normal volunteers and in patients with Alzheimer's disease. J Psychiatr Res. 1999; 33: 397-405.

75. Chao CC, Ala TA, Hu S, Crossley KB, Sherman RE, Peterson PK, et al. Serum cytokine levels in patients with Alzheimer's disease. Clin Diagn Lab Immunol. 1994; 1: 433-436.

76. Mocali A, Cedrola S, Della Malva N, Bontempelli M, Mitidieri VA, Bavazzano A, et al. Increased plasma levels of soluble CD40, together with the decrease of TGF beta 1, as possible differential markers of Alzheimer disease. Exp Gerontol. 2004; 39: 1555-1561.

77. De Luigi A, Fragiacomo C, Lucca U, Quadri P, Tettamanti M, Grazia De Simoni M, et al. Inflammatory markers in Alzheimer's disease and multi-infarct dementia. Mech Ageing Dev. 2001; 122: 1985-1995.

78. Pirttila T, Mehta PD, Frey H, Wisniewski HM. Alpha 1-antichymotrypsin and IL-1 beta are not increased in CSF or serum in Alzheimer's disease. Neurobiol Aging. 1994; 15: 313-317.

79. Rosenberg PB. Clinical aspects of inflammation in Alzheimer's disease. Int Rev Psychiatry. 2005; 17: 503-514.

80. Tarkowski E, Blennow K, Wallin A, Tarkowski A. Intracerebral production of tumor necrosis factor-alpha, a local neuroprotective agent, in Alzheimer disease and vascular dementia. J Clin Immunol. 1999; 19: 223-230.

81. Engelborghs S, De Brabander M, De Crée J, D'Hooge R, Geerts H, Verhaegen H, et al. Unchanged levels of interleukins, neopterin, interferon-gamma and tumor necrosis factor-alpha in cerebrospinal fluid of patients with dementia of the Alzheimer type. Neurochem Int. 1999; 34: 523-530.

82. Holmes C, Cunningham C, Zotova E, Culliford D, Perry VH. Proinflammatory cytokines, sickness behavior, and Alzheimer disease. Neurology. 2011; 77: 212-218.

83. Guerreiro RJ, Santana I, Bras JM, Santiago B, Paiva A, Oliveira C. Peripheral inflammatory cytokines as biomarkers in Alzheimer's disease and mild cognitive impairment. Neurodegener Dis. 2007; 4: 406-412.

84. Gezen-Ak D, Dursun E, Hanağası H, Bilgiç B, Lohman E, Araz ÖS, et al. BDNF, TNFα, HSP90, CFH, and IL-10 serum levels in patients with early or late onset Alzheimer's disease or mild cognitive impairment. J Alzheimers Dis. 2013; 37: 185-195.

85. Alvarez XA, Franco A, Fernández-Novoa L, Cacabelos R. Blood levels of histamine, IL-1 beta, and TNF-alpha in patients with mild to moderate Alzheimer disease. Mol Chem Neuropathol. 1996; 29: 237-252.

86. Angelopoulos P, Agouridaki H, Vaiopoulos H, Siskou E, Doutsou K, Costa V, et al. Cytokines in Alzheimer's disease and vascular dementia. Int J Neurosci. 2008; 118: 1659-1672.

87. Alsadany MA, Shehata HH, Mohamad MI, Mahfouz RG. Histone deacetylases enzyme, copper, and IL-8 levels in patients with Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2013; 28: 54-61.

88. Xia M, Qin S, McNamara M, Mackay C, Hyman BT. Interleukin-8 receptor B immunoreactivity in brain and neuritic plaques of Alzheimer's disease. Am J Pathol. 1997; 150: 1267-1274.

89. Zhang J, Sokal I, Peskind ER, Quinn JF, Jankovic J, Kenney C, et al. CSF multianalyte profile distinguishes Alzheimer and Parkinson diseases. Am J Clin Pathol. 2008; 129: 526-529.

90. Zuliani G, Guerra G, Ranzini M, Rossi L, Munari MR, Zurlo A, et al. High interleukin-6 plasma levels are associated with functional impairment in older patients with vascular dementia. Int J Geriatr Psychiatry. 2007; 22: 305-311.

91. Ray S, Britschgi M, Herbert C, Takeda-Uchimura Y, Boxer A, Blennow K, et al. Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. Nat Med. 2007; 13: 1359-1362.

92. Doecke JD, Laws SM, Faux NG, Wilson W, Burnham SC, Lam CP, et al. Blood-based protein biomarkers for diagnosis of Alzheimer disease. Arch Neurol. 2012; 69: 1318-1325.

93. Soares HD, Potter WZ, Pickering E, Kuhn M, Immermann FW, Shera DM, et al. Plasma biomarkers associated with the apolipoprotein E genotype and Alzheimer disease. Arch Neurol. 2012; 69: 1310-1317.

94. Paquet C, Boissonnot M, Roger F, Dighiero P, Gil R, Hugon J. Abnormal retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. Neurosci Lett. 2007; 420: 97-99.

95. Mandal PK, Joshi J, Saharan S. Visuospatial perception: an emerging biomarker for Alzheimer's disease. J Alzheimers Dis. 2012; 31 Suppl 3: S117-135.

96. Podlesniy P, Figueiro-Silva J, Llado A, Antonell A, Sanchez-Valle R, Alcolea D, et al. Low cerebrospinal fluid concentration of mitochondrial DNA in preclinical Alzheimer disease. Ann Neurol. 2013; 74: 655-668.

97. Perry G, Friedman R, Shaw G, Chau V. Ubiquitin is detected in neurofibrillary tangles and senile plaque neurites of Alzheimer disease brains. Proc Natl Acad Sci U S A. 1987; 84: 3033-3036.

98. Simonsen AH, McGuire J, Hansson O, Zetterberg H, Podust VN, Davies HA, et al. Novel panel of cerebrospinal fluid biomarkers for the prediction of progression to Alzheimer dementia in patients with mild cognitive impairment. Arch Neurol. 2007; 64: 366-370.

99. Kandimalla RJ, Anand R, Veeramanikandan R, Wani WY, Prabhakar S, Grover VK, et al. CSF ubiquitin as a specific biomarker in Alzheimer's disease. Curr Alzheimer Res. 2014; 11: 340-348.

100. Mapstone M, Cheema AK, Fiandaca MS, Zhong X, Mhyre TR, MacArthur LH, et al. Plasma phospholipids identify antecedent memory impairment in older adults. Nat Med. 2014; 20: 415-418.

101. Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, et al. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science. 2003; 299: 256-259.

102. Lin X, Parisiadou L, Sgobio C, Liu G, Yu J, Sun L, et al. Conditional expression of Parkinson's disease-related mutant alpha-synuclein in the midbrain dopaminergic neurons causes progressive neurodegeneration and degradation of transcription factor nuclear receptor related 1. J Neurosci. 2012; 32: 9248-9264.

103. Chahine LM, Stern MB, Chen-Plotkin A. Blood-based biomarkers for Parkinson's disease. Parkinsonism Relat Disord. 2014; 20 Suppl 1: S99-103.

104. Schwarzschild MA, Schwid SR, Marek K, Watts A, Lang AE, Oakes D, et al. Serum urate as a predictor of clinical and radiographic progression in Parkinson disease. Arch Neurol. 2008; 65: 716-723.

105. Chen-Plotkin AS, Hu WT, Siderowf A, Weintraub D, Goldmann Gross R, Hurtig HI, et al. Plasma epidermal growth factor levels predict cognitive decline in Parkinson disease. Ann Neurol. 2011; 69: 655-663.

106. Goldstein DS, Holmes C, Sharabi Y. Cerebrospinal fluid biomarkers of central catecholamine deficiency in Parkinson's disease and other synucleinopathies. Brain. 2012; 135: 1900-1913.

107. Qiang JK, Wong YC, Siderowf A, Hurtig HI, Xie SX, Lee VM, et al. Plasma apolipoprotein A1 as a biomarker for Parkinson disease. Ann Neurol. 2013; 74: 119-127.

108. Parnetti L, Balducci C, Pierguidi L, De Carlo C, Peducci M, D'Amore C, et al. Cerebrospinal fluid beta-glucocerebrosidase activity is reduced in Dementia with Lewy Bodies. Neurobiol Dis. 2009; 34: 484-486.

109. Ewers M, Buerger K, Teipel SJ, Scheltens P, Schröder J, Zinkowski RP, et al. Multicenter assessment of CSF-phosphorylated tau for the prediction of conversion of MCI. Neurology. 2007; 69: 2205-2212.

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