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CSF Biomarkers in Parkinson's Disease

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1. Introduction

1.1 Do we need biological markers for Parkinson's disease?

In the recent years increasing attention on biomarkers for neurodegenerative diseases, including Parkinson's disease (PD), has been paid.

The reasons of this growing tendency are several:

(i) PD is one of the most common neurodegenerative diseases, affecting approximately 1% of people over 60 years of age (Samii et al., 2004). Diagnosis of PD is based on clinical criteria, relying on motor features: rigidity, bradykinesia, resting tremor and in the late stages postural instability (Hughes et al., 1992). However, clinical diagnosis especially in the early stages of disease can be challenging owing to the difficult differential diagnosis with essential tremor and atypical parkinsonism, namely multiple system atrophy (MSA), progressive sopranuclear palsy (PSP), and corticobasal degeneration (CBD). Although in movement disorder specialized settings the diagnostic accuracy is satisfactory (≥80%), almost one third of the clinical diagnoses in patients with parkinsonism is revised in the first five years of disease (Hughes et al., 2002). Diagnostic accuracy in the early stages of disease is important, in view of forthcoming disease-modifying therapies (Olanow et al., 2008). In this perspective, diagnostic biomarkers are urgently needed. (ii) Also, there is the need for progression biomarkers, ie, parameters reflecting a feature associated with disease- severity (Maetzler et al., 2009). (iii) Finally, PD per se is a heterogeneous disease, with different clinical phenotypes (the akinetic-rigid type vs. the tremor dominant variant) and different etiologies (genetic vs. sporadic form), which might have different progression rate, prognosis, thus requiring different therapeutic approaches. PD is not merely a motor disorder.

Recently, great attention has been drawn to non-motor symptoms, namely cognitive decline, behavioural changes, sleep disorders and autonomic dysfunction, due to their relevant impact on quality of life of parkinsonian patients (Chaudhuri et al., 2006). Both in early and in advanced stages, these symptoms represent a challenge in the clinical management of PD

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patients. Among non-motor features, i.e. hyposmia and R.E.M. sleep behavior disorders (RBD), cognitive decline dramatically changes the prognosis of disease. In this perspective, a biomarker distinguishing parkinsonian patients who will develop cognitive decline from those who will not, would have a great impact. Moreover, cognitive performances are impaired not only in PD but also in other parkinsonism, such as PSP or dementia with Lewy bodies (DLB), and again a biomarker differentiating these neurodegenerative diseases is required.

In order to develop a specific and successful treatment, the tendency to group together parkinsonism solely on a clinical ground should be replaced by the systematic use of reliable and validated biomarkers as the peripheral expression of the underlying pathogenetic mechanisms (Schlossmacher and Mollenhauer, 2010). In medicine biomarkers have different purposes: to identify subjects at risk of developing a certain disease (marker of trait); to identify the manifestation of disease (marker of state); to reflect the progression of disease (progression marker); to predict the onset of disease (marker of fate) (Schlossmacher and Mollenhauer, 2010). In this perspective, biomarkers are needed in order to reach an early and accurate PD diagnosis, also allowing a differential diagnosis between PD and other parkinsonism; to differentiate PD with dementia from Alzheimer's disease (AD), DLB and other dementias; to differentiate between variants of PD; to monitor disease progression and treatment response (Nyhlén et al., 2010).

An ideal biomarker should be sensitive, reproducible, closely associated to the disease process, easy to measure, inexpensive, non-invasive and thoroughly validated (Michell et al., 2004; van Dijk et al., 2010). Unfortunately such a marker is not available yet in PD.

Potential biomarkers in PD include imaging markers, such as striatal dopamine transporter binding measured with single photon emission computed tomography (Isaias and Antonini, 2010), transcranial ultrasound (Berg and Becker, 2002), or body fluid markers. Although many efforts have been made to detect reliable biomarkers in blood and urine, the most promising source of biomarkers is cerebrospinal fluid (CSF). The main advantage of CSF is its direct contact with brain so that it is thought that biochemical alterations in the brain are reflected in CSF. This is one of the reasons why CSF is the main source of biomarkers also in other neurodegenerative diseases, such as Alzheimer's disease, where it has become of support in early diagnosis (Dubois et al., 2007; Dubois et al., 2010).

This chapter will be dedicated to candidate CSF biomarkers in PD. However, some considerations should be taken in account while reviewing CSF studies in neurodegenerative disease and specifically in PD. CSF proteins pool is formed by a main part of blood-derived proteins and a minor part of brain tissue protein (Mollenhauer and Trenkwalder, 2009; van Dijk et al., 2010). Special attention should be driven on technical aspects in the collection of CSF, particularly to avoid blood contamination during lumbar puncture, which can enormously increase CSF content of protein owing to the high concentration of proteins in blood (Hong et al., 2010), and to limit circadian fluctuations of protein concentrations (Nilsson et al., 1992).

In this section we will consider α-synuclein, the main component of Lewy bodies; molecules expressing mitochondrial dysfunction and oxidative stress, such as DJ-1, and other oxidative stress related proteins; molecules reflecting impaired protein degradation, protein aggregation and LBs formation, such as protein tissue transglutaminase, osteopontine, and neurofilaments; molecules reflecting inflammation, glial activation, apoptosis and cell death. Also, classical CSF AD biomarkers - β-amyloid$_{1-42}$ (Aβ_{1-42}) , total tau, hyperphosphorylated tau – and their correlation with cognitive impairment in PD will be discussed.

2. Alpha-synuclein as disease-state marker

The neuropathological hallmarks of PD are the loss of pigmented neurons in the substantia nigra pars compacta (SNpc) and the Lewy bodies, LBs (Braak et al., 2003). LBs are intraneuronal spherical inclusions, which appear eosinophilic with a dense core surrounded by a halo at hematoxylin/eosin staining (Shults, 2006). LBs' main component is α-synuclein (α-syn), a 140-amino acids protein mainly located in the presynaptic terminals of most neurons. It is a member of a highly conserved family of proteins consisting of α-, β-, and γ-syn (Spillantini et al., 1997, Eriksen et al., 2003). Alpha-syn consists of: i) the N-terminal region, which contains a number of imperfect repeats, with the consensus motif KTKEGV; ii) the central hydrophobic region, called NAC (non-amyloid component), suggested to be responsible for the aggregation process (Giasson et al., 2001); and iii) the acidic C-terminal region involved in the regulation of fibril formation (Murray et al., 2003). Several studies suggest that α-syn exists in equilibrium between a cytosolic unfolded conformation and a membrane-bound, alpha-helical structure (Cole et al., 2002; McLean et al., 2000). Although its physiological function is still unknown, its localization and ability to interact with membranes suggest that α-syn might play a role in vesicle dynamics and trafficking at the presynaptic terminal and in brain lipid metabolism (Willingham et al. 2003; Darios et al., 2010).

Inclusions of α-syn are neuropathological features also in other neurodegenerative diseases that, together with PD, form the spectrum of synucleinopathies. They include multiple system atrophy (MSA), an oligodendrogliopathy, and DLB, the most frequent cause of degenerative dementia after AD (Spillantini & Goedert, 2000; Galvin et al., 2001). The discovery of missense mutations (Polymeropoulos et al., 1997; Kruger et al., 1998; Zarranz et al., 2004) and multiplications (duplications and triplications) (Chartier-Harlin et al., 2004; Singleton et al., 2003) within the gene encoding α-syn (*SNCA*) in familial case of PD has further increased the interest on this protein implicated in the etiopathogenesis of PD. More recently, *SNCA* polymorphisms have been associated with increased risk of sporadic PD and MSA, reinforcing the hypothesis of its implication in the etiopathogenesis of synucleinopathies (Simón-Sánchez et al., 2009; Satake et al., 2009; Scholz et al., 2009). Despite these evidences of a direct implication of α-syn in the pathogenesis of PD, the mechanisms through which this happens are not so clear. The lack of pathological phenotype associated to α-syn knock-out mice (Chandra et al., 2004) together with the observation of familial PD cases related to duplications/triplications of α-syn, as well as the presence of α-syn aggregates in PD brains, suggest for α–syn a gain-of-function pathogenetic mechanism. In line with this view, it has been shown that α-syn tends to aggregate into amyloid-like, beta-sheet fibrils (Bisaglia et al., 2009) and fibrillization is increased in the presence of mutations or elevated protein levels (Conway et al., 2001; Li et al., 2001; Shtilerman et al., 2002).

In PD and other synucleinopathies, α-syn in its monomeric form tends to aggregate into insoluble fibrils. Soluble oligomers and α-syn protofibrils, the intermediate stages in the development of these aggregates, are considered to be the toxic forms of α-syn (El-Agnaf et al., 2003a). Several factors such as phosphorylation at Ser129, decrease in pH, temperature increase, presence of metal ions and small charged molecules influence fibril formation and aggregation (Uverski 2007). Aggregation of α-syn can be promoted also by the protein tissue transglutaminase, which induces crosslinkings (Junn et al., 2003).

Alpha-syn degradation is mediated mainly through proteasomal system and autophagy pathway via lysosomes. Self-digestion of protein via lysosomes activity can occur in a chaperon-dependent or -independent way (Cuervo et al., 2004; Shin et al., 2005; Lee et al., 2005).

3. Is CSF alpha-syn a diagnostic marker of PD and other synucleynopathies?

Several studies have detected α-syn in human biological fluids, including plasma and CSF (El-Agnaf et al., 2003b; Lee et al., 2005; Mollenhauer et al., 2008; Mollenhauer et al., 2010). More recently attention has been focused on CSF α-syn as potential biomarker (see table 1).

The presence of α-syn in the CSF was first reported in 2000 using an immunoprecipitation and immunoblotting approach with the limit of low specificity (Borghi et al. 2000). In another study CSF collected at autopsy was analyzed, thus raising the concern of a possible increase of α-syn due to autolysis (El-Agnaf et al., 2003b). Finally the proof of the presence of α-syn in CSF was provided using affinity enrichment of CSF followed by mass spectrometry (Mollenhauer et al., 2008). In the last years, several studies on CSF α-syn as potential biomarker of synucleinopathy have been published, but the results have remained so far inconclusive, mainly owing to differences in sample handling and in measurement methods. The wide range of absolute concentration reported even in the same group of patients has been a hindrance to the interpretation of results (Mollenhauer et al., 2010). Another concern is the possible contamination of CSF sample with blood during lumbar puncture. Indeed, since levels of α-syn stored in human blood cells are much higher than in CSF, minimal contamination of CSF with blood may increase CSF α-syn concentration (Hong et al., 2010). Neither rostrocaudal gradient nor diurnal fluctuations of α-syn CSF concentrations have been found so far (Hong et al., 2010; Mollenhauer et al., 2010). Other possible confounders in CSF α-syn levels are age and total CSF protein content. These parameters have been only partially investigated. Some studies have shown some negative correlation of α-syn with age (Mollenhauer et al., 2008; Tokuda et al., 2006; Ohrfelt et al., 2009; Noguchi-Shinohara et al., 2009; Parnetti et al., 2011), whereas one study (Hong et al., 2010) reported an opposite trend. In some studies reduced levels of α-syn in CSF from PD and DLB have been detected compared to controls or AD (Tokuda et al., 2006; Mollenhauer et al., 2008; Tokuda et al., 2010; Kasuga et al., 2010; Hong et al., 2010; Parnetti et al., 2011). Conversely, in other studies no significant difference between groups was observed (Öhrfelt et al., 2009; Noguchi-Shinohara et al., 2009; Spies et al., 2009).

Recently we investigated CSF concentration of α-syn and classical CSF biomarkers - Aβ1-42, total tau, phosphorylated tau - in patients with PD (n. 38), DLB (n. 32), AD (n. 48), frontotemporal dementia (n. 31) and in age-matched controls (n. 32). Results show that α-syn are significantly lower in all pathological groups as compared to controls, whereas the total tau/α-syn and phosphorylated tau/α-syn ratios were significantly lower only in PD. Our study supports that α-syn alone has a low specificity for PD, but a better performance can be achieved with the ratio total tau/α-syn (Parnetti et al., 2011). This finding strengthens the need of measuring different biomarkers in order to better know the neurochemical profile of neurodegenerative diseases.

To shed further light into this complex scenario a large study including 721 patients has been recently published (Mollenhauer et al., 2011). In this study CSF α-syn and tau levels were measured in both synucleinopathies (PD, DLB, MSA) and tauopathies (AD, PSP). The study has been conducted in three cohorts of patients: a "training set" from the collaboration of three centres; a validation cohort; and an-autopsy-confirmed group of AD, DLB and controls (table 1). This work confirms that synucleinopathies are characterized by lower concentrations of CSF α-syn. However, since the specificity of α-syn alone is low, the combination of CSF α-syn and tau increases the discriminative power for differentiating PD

Table 1. Overview of the studies published on CSF determination of total alpha-synuclein.

Study	Patients	Quantification methods	Capturing Ab (binding site)	Reading Ab (b site)
Tokuda et al., 2006	33 PD, 38 controls	Direct sandwich ELISA	mAb 211 (aa 121-125)	pAb FL-140 (fu length)
Mollenhauer et al., 2008	8 PD, 38 DLB, 13 AD, 8 CJD, 13 controls	Direct sandwich ELISA (384-well plates)	pAb mSA-1 (full length)	mAb Syn1 (aa
Ohrfelt et al., 2009	15 DP, 15 DLB, 66 AD, 55 healthy controls	Indirect and amplified sandwich ELISA	mAb Syn1 (aa 84-96)	Syn 5d (aa 127
Noguchi-Shinohara et al., 2009	16 DLB, 21 AD	Direct sandwich ELISA	mAb 211 (aa 121-125)	pAb FL-140 (fu length)
Spies et al., 2009	40 DLB, 131 AD, 28 VaD, 39 FTD	Direct sandwich ELISA	mAb 211 (aa 121-125)	pAb FL-140 (fu length)
Hong et al., 2010	117 PD, 50 AD, 132 healthy controls	xMAP analysis	mAb LB 509 (aa 115-124)	mAb 211 (aa 1
Kasuga et al., 2010	34 DLB, 31 AD, 21 other dementias, 2 SNCA duplication	Direct sandwich ELISA	mAb Syn1 (aa 84-96)	pAb FL-140 (fu length)
Tokuda et al., 2010	32 PD, 18 control & 25 PD, 35 AD, 18 PSP, 43 controls	Direct sandwich ELISA (for α-syn oligomers ELISA 384-well plate)	mAb 211 (aa 121-125)	pAb FL-140 (fu length)
Parnettin et al., 2011	38 PD, 32 DLB, 48 AD, 31 FTD, 32 neurological controls	Direct sandwich ELISA	mAb 211 (aa 121-125)	pAb FL-140 (fu length)
Mollenhauer et al., 2011	721 pts from 3 cohorts: (a) 62 AD, 76 controls, 55 DLB, 51 PD, 29 AD; (b) 23 controls, 22 NPH, 8 PSP, 66 DLB, 273 PD, 15 MSA; (c) 21 AD, 7 controls, 13 DLB	Direct sandwich ELISA (384-well plates)	mAb Syn1-BB	pAb mSA-1 (fu length)

from the other neurodegenerative diseases. The major merits of the study by Mollenhauer and colleagues are the large sample size and the completeness of the range of synucleinopathies assessed, allowing us to be more confident of the interpretation of the results obtained by the measurement of total CSF α-synuclein. It also confirms the reliability of the assay, fixing the cutoff value at 1.6 pg/μL—ie, lower levels strongly suggest the presence of a synucleinopathy. This achievement is likely to be fundamental to the systematic use of α-synuclein as a biomarker in a clinical setting (Parnetti, 2011).
Another perspective, which highlights the direction toward a combination of biomarkers rather than toward a single marker, is the combination of CSF total α-syn and α-syn oligomers, with the latter found increased in PD in two recent papers (Paleologou et al., 2009; Tokuda et al., 2010). Whether α-syn is a marker of trait or a marker of progression is under investigation. According to the knowledge so far collected no clear-cut correlation with disease duration or disease severity (Hong et al., 2010; Parnetti et al., 2011) has been highlighted, suggesting that decrease of CSF α-syn is a marker of trait in synucleinopathies.

4. Other possible CSF biomarkers of PD: CSF proteins reflecting PD pathogenesis

Beyond α-syn, several other proteins and molecules have been investigated as potential biomarkers in PD. Most of them reflect PD pathogenesis and are classified upon different pathogenetic mechanisms.

4.1 Molecules expressing mitochondrial dysfunction and oxidative stress

The evidences for the implication of mitochondrial dysfunction and increased oxidative stress in the pathogenesis of PD are several (Schapira, 2008; Van Dijk et al., 2010): (i) mitochondrial complex I activity is reduced in the substantia nigra (Schapira et al., 1989); (ii) MPTP and rotenone toxicity is mediated via mitochondrial complex I inhibition (Tipton & Singer, 1993; Betarbet et al., 2003); (iii) mitochondrial-related proteins, such as prohibitin, ATP synthase and superoxide dismutase (SOD2), are altered in the nigra and frontal cortex of PD patients (Ferrer et al., 2007); and (iv) some monogenic forms of PD are caused by mutations of DJ-1 (Bonifati et al., 2003), PINK-1 (Valente et al., 2004), LRRK2 (Paisán-Ruíz et al., 2004; Zimprich et al., 2004), all implicated in the mitochondrial function and oxidative stress (Lin & Beal, 2006).
Thus, attention has been focused on markers linked to the mitochondrial dysfunction and oxidative stress.

4.1.2 DJ-1

CSF DJ-1 levels have been investigated in two studies, yielding opposite results (Waragai et al., 2006; Hong et al., 2010). Waragai et al. (2006) found increased CSF DJ-1 levels (assessed by means of western blotting) in PD-patients (n. 40) as compared to controls (n. 38). More recently, in a larger study involving PD (n. 117), controls (n. 132) and AD (n. 50), using a multiplex technology, CSF DJ-1 concentrations were found to be decreased in the PD group (Hong et al., 2010). Similarly for what found for α-syn, DJ-1 levels were influenced by blood contamination. Also CSF levels were correlated with age and not with disease severity (Hong et al., 2010). Divergent results in the two studies might be mostly due to different methods.

4.1.3 Other oxidative stress related proteins

Other oxidative stress related proteins have been investigated in the CSF of PD patients, with the limits of single observations, small sample size, inconclusive results and lack of disease specificity.

Increased CSF concentration of nitrated manganese superoxide dismutase (Mn-SOD) in PD, AD and amyotrophic lateral sclerosis (ALS) have been reported (Aoyama et al., 2000). Another study investigating oxidative stress in PD, AD, ALS and Huntington's disease (HD) found decreased Cu/Zn-dependent superoxide dismutase (SOD1) activity in all these diseases (Boll et al., 2008); also, an increase of modified forms of Cu/Zn-dependent SOD has been published (Guo et al., 2009). Other studies found reduced CSF concentration of ceruloplasmin and ferroxidase activity, the enzyme that catalyzes the conversion of Fe^{2+} in Fe^{3} (Boll et al., 1999; Boll et al., 2008; Abdi et al. 2006), whereas CSF transferrin levels where unchanged in PD (Loeffler et al., 1994; van Kamp et al., 1995).

4.2 Impaired protein degradation

Impaired protein degradation, leading to aggregation of misfolded, mutant and toxic variant of proteins, plays a key role in the pathogenesis of PD and neurodegenerative diseases. Two main systems are implicated in protein degradation, namely the lysosomal and the ubiquitin-proteasome systems. Autophagy is a crucial pathway for the degradation of α-syn (Cuervo et al., 2004; Shin et al., 2005; Lee et al., 2005). In recent years a strong link between mutations in glucocerebrosidase gene (GBA), the gene implicated in Gaucher disease (GD), and PD has been discovered supporting the link between lysosomal system and pathogenesis of PD (DePaolo et al., 2009; Velayaty et al., 2010). GD is an autosomal recessive lipidosis resulting from a deficiency of glucocerebrosidase enzyme. The observation of patients with GD and parkinsonism (Tayebi et al., 2003, Goker-Alpan et al., 2008), the increased rate of GBA mutations and polymorphism in PD patients (Sidransky et al., 2009) along with neuropathological findings in brain of GD patients with parkinsonism similar to PD and DLB, all strengthening this hypothesis. The deficit in GBA might act through an impaired degradation of proteins via lysosomes leading to abnormal protein aggregates and Lewy bodies formation. Moving from these observations, in the last years we studied the activities of CSF beta-glucocerebrosidase and others lysosomal enzymes, finding that alpha-mannosidase, beta-mannosidase, and more evidently glucorebrosidase, were significantly reduced in PD (Balducci et al., 2007) and, even more markedly, in DLB patients (Parnetti et al., 2009).

4.3 Protein aggregation and Lewy body formation

One of the neuropathological hallmarks of PD is inclusions of misfolded, mutant, and damaged proteins and the formation of Lewy bodies (LBs) and Lewy neurites (LN) (Shults, 2006). The main component of LBs is α-synuclein (α-syn). As described previously, α-syn tends to aggregate into toxic oligomers and α-syn protofibrils, the intermediate stages of insoluble fibrils (El-Agnaf et al., 2003a). The aggregation of α-syn is modulated by several factors and promoted by the protein tissue transglutaminase, a regulator of apoptosis that appears to modulate α-syn oligomerization promoting crosslinkings. A study investigating CSF tissue transglutaminase levels in 54 PD-patients and in 34 controls found increased levels only in PD (Vermes et al., 2004).

Several other proteins are present in Lewy bodies, such as osteopontin and neurofilaments.

Osteopontin is a protein involved in apoptosis and oxidative stress, identified in several neurodegenerative diseases, including AD (Simonsen et al., 2007) and shown to be increased in CSF of PD patients as compared to controls (Maetzler et al., 2007).
Neurofilaments are component of the cytoskeleton. In PD both light and heavy chain neurofilaments have been shown to be unchanged compared to controls, whereas they have been found to be elevated in other parkisonism, including MSA and progressive sopranuclear palsy (PSP) (Abdo et al., 2007; Holmberg et al., 1998). These observations have suggested that neurofilaments might be a promising marker in the differential diagnosis of parkinsonism.

4.4 Inflammation and glial activation

Among the several molecular and cellular changes leading to cellular death in PD, neuroinflammatory mechanisms seem to play an important contribution (Hirsch & Hunot, 2009). Post-mortem studies have shown microglial activation, astrogliosis, and lymphocytic infiltration in the nigra of PD patients (Mc Geer et al., 1988; Damier et al., 1993). Increased concentrations of TNF-α, β2-microglobulin, epidermal growth factor (EGF), transforming growth factor α (TGF-α), TGF-β1, and interleukins 1β, 6 and 2 have been detected in the striatum of PD (Mogi et al., 1994a; Mogi et al., 1994b; Mogi et al., 1995a; Mogi et al., 1995b; Mogi et al., 1996a). Some CSF studies have tried to investigate the involvement of inflammatory mechanisms in PD. Increased levels of interleukins, including interleukin 1β, interleukin-8 and 6, and decreased levels of components of complement have been detected in CSF of PD patients (Mogi et al., 1995a; Blum-Degen et al., 1995; Müller et al., 1998; Finehout et a., 2005; Guo et al., 2009). However, it is still unclear whether these changes are the cause or the consequence of neuronal degeneration (Hirsch & Hunot, 2009). Moreover, these changes are not disease specific, being shared by many neurodegenerative diseases. A recent study, carried out in a large cohort including PD (n. 126), MSA (n. 32), AD (n. 50), and controls (n. 137), showed significantly lower CSF levels of the cytokine Flt3 ligand in MSA patients as compared to PD subjects (Shi et al., 2011).

4.5 Apoptosis and cell death

Apoptosis is an important mechanism of cell death in neurodegenerative diseases, including PD, as supported by a neuropathological study showing apoptotic process in 8 out of 11 midbrains from PD patients (Mochizuki et al., 1996). Moreover, the anti-apoptotic protein bcl-2, the apoptosis-signaling receptor Fas, and the Annexin V have been found to be increased in the substantia nigra of PD (Mogi et al. 1996b; Mogi et al., 1996c; Werner et al., 2008). A CSF study showed lower levels of Annexin V in PD as compared to controls. This result was interpreted as the consequence of the consumption of this protein during neuronal apoptosis in PD (Vermes et al., 1999). CSF study targeting bcl2 and Fas have failed, since neither bcl2 nor Fas are measurable in CSF (Mogi et al. 1996b; Mogi et al. 1996c).

5. Classical CSF biomarkers and risk of cognitive impairment in PD

The prevalence of cognitive impairment in PD-patients is higher compared to general population (30%) even in early PD (Aarsland et al., 2009; Aarsland & Kurz 2010), and the risk of dementia dramatically increases over the course of disease occurring in up to 80% of patients after 20 years of follow-up (Hely et al., 2008). Cognitive impairment and dementia

represent one of the most disabling non-motor symptoms in PD, with a relevant impact on quality of life of patients and caregivers. The spreading of Lewy body pathology to neocortical regions altogether with AD-type pathology in terms of β-amyloid deposits, have been implicated in the pathogenesis of cognitive decline in PD (Braak et al., 2005; Ballard et al., 2006), suggesting an interplay between synucleinopathies and tauopathies. Recently, a growing amount of investigations in PD has focused on CSF biomarkers traditionally used in AD, namely β-amyloid$_{1-42}$ (Aβ $_{1-42}$), total tau, hyperphosphorylated tau, in order to improve the ability to detect risk for cognitive impairment and dementia (Sjögren et al., 2002; Mollenhauer et al., 2006; Parnetti et al., 2008; Compta et al., 2009; Alves et al., 2010; Siderowf et al., 2010; Montine et al., 2010; Leverenz et al., 2011) (table 2). Tau protein, a microtubule associated protein, in its phosphorylated form represents the major component of the neurofibrillary tangles (Grundke-Iqbal et al., 1986). Increased CSF levels of tau and phosphorylated tau have been found to be specific markers for AD (Blennow et al., 1995). The different enzymatic cleavage of the 120kDa transmembrane amyloid precursor protein (APP) by three different secretases produces different β-amyloid peptides (Glenner et al., 1984). Beta-amyloid$_{1-42}$ peptide (Aβ $_{1-42}$), the main component of amyloid plaques in the brain of patients with AD and DLB, has been shown to be decreased in the CSF of AD patients for the first time in 1995 (Motter et al, 1995). These findings have lead to a revision of the National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders (NINCDS-ADRDA) criteria for the diagnosis of AD including CSF biomarkers (Dubois et al., 2007). Studies report normal CSF levels of tau and phosphorylated tau in PD (Blennow et al., 1995; Parnetti et al., 2008; Alves et al., 2010; Shi et al., 2010), whereas unchanged or slightly decreased levels of Aβ $_{1-42}$ have been reported (Sjögren et al., 2002; Mollenhauer et al., 2006; Bibl et al., 2006; Parnetti et al., 2008; Compta et al., 2009; Alves et al., 2010; Siderowf et al., 2010; Montine et al., 2010; Leverenz et al., 2011; Shi et al., 2011). More recently, several studies have been published reporting a possible association between low Aβ $_{1-42}$ levels and cognitive impairment in PD (Compta et al., 2009; Alves et al., 2010; Siderowf et al., 2010; Montine et al., 2010; Leverenz et al., 2011). Lower levels of CSF Aβ $_{1-42}$ were found in 20 PD-patients with dementia compared to 20 PD-patients and 30 controls, whereas higher concentrations of CSF tau and phosphorylated tau were associated with impaired memory and naming, suggesting an underlying AD pathology in PDD (Compta et al., 2009). A recent study compared CSF concentrations of Aβ$_{1-42}$, Aβ$_{1-40}$, Aβ $_{1-38}$, total tau and phosphorylated tau in a large cohort of de novo and untreated PD-patients (n. 109), recruited from the Norwegian ParkWest study, with those of 36 age-matched controls and 20 mild AD patients (Alves et al., 2010). In PD patients reduced levels of Aβ $_{1-42}$, Aβ $_{1-40}$, Aβ $_{1-38}$ compared to controls were found. Authors showed also a significant association between CSF levels of Aβ $_{1-42}$, Aβ $_{1-40}$, Aβ $_{1-38}$ and memory impairment. A recent prospective study in a cohort of 45 PD patients with 1-year follow-up showed that lower levels of Aβ $_{1-42}$ at baseline were associated with a more rapid cognitive decline (Siderowf et al., 2010). Another recent study reported an association between low levels of Aβ $_{1-42}$ levels in 22 non-demented PD patients and worse performance at Digit Symbol test (Leverenz et al., 2011). Although the limitations of these studies, including the small sample size, the heterogeneity of clinical features of patients, the lack of a group of control, the results are interesting and support the role of amyloid plaques in the pathogenesis of dementia in PD patients, in line with a recent report of altered in vivo amyloid imaging in 2 autopsy-confirmed PDD patients (Burack et al., 2010).

Study	Patients	CSF Aβ42	CSF T-tau	CSF P-tau	Relationship with cognitive impairment
Parnetti et al., 2008	20 PD, 18 PDD, 19DLB, 20 controls	CTRL>PD> PDD>DLB	CTRL=PD DLB>PDD> PD	CTRL=PD, PDD,DLB	↓ Aβ42 associated with ↓ performance at Word Fluency and Prose Memory tests
Compta et al., 2009	20 PD, 20 PDD, 30 controls	CTRL>PD> PDD	CTRL=PD PDD>PD	CTRL=PD PDD>PD	↓ Aβ42 in patients with ↓ performance at Verbal Fluency test
Siderowf et al., 2010	45 PD, no controls	= = =	= = =	= = =	↓ baseline Aβ42 associated with faster cognitive decline (↓Aβ42 independent predictor of cognitive decline)
Alves et al., 2010	109 de novo PD, 36 controls	PD<CTRL	CTRL=PD	CTRL=PD	↓ Aβ42 associated with poorer performances on memory tests
Leverenz et al., 2011	22 PD, no controls	= = =	= = =	Not measured	Association between ↓Aβ42 and/or Aβ42/T-tau and ↓ performance at Digit Symbol and Category Fluency tests

Table 2. CSF Aβ42 and cognitive impairment in PD.

6. Conclusions and perspectives

Neurodegenerative diseases, including PD, are common and become more common with increasing age. At present, diagnosis substantially relies on clinical criteria, which makes it difficult to achieve an accurate early diagnosis. Moreover, it is not rare that in an elderly patient two or more neurodegenerative diseases, as well as cerebrovascular changes, coexist (Nyhlen et al., 2010). It is also possible that conceptually distinct disease processes may reinforce or modify each other. For example, α-syn aggregation may promote Ab aggregation and *vice versa;* also, tau has been shown to interact with α-syn, promoting its fibrillization. It can be claimed that PD- and AD-like changes often occur simultaneously, contribute to the clinical symptoms and make it difficult to identify the underlying pathology based only on clinical phenotype changes. In this context, the systematic assessment of CSF biomarkers may be of help, also suggesting the possibility to adopt a different nomenclature for identifying distinct disease-associated processes rather than the single disease.

In view of available disease-modifying drugs able to directly interfere with the etiopathogenetic events – ie, anti-amyloid agents; inhibitors of tau or α-syn phosphorylation, etc. - early diagnosis is mandatory for all neurodegenerative diseases. This concept is even more important when considering clinically heterogeneous disorders as PD is. At present,

we have promising candidate biomarkers, which also guarantee to reliably exclude other diagnoses than PD.

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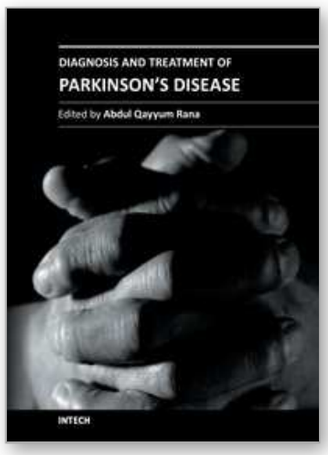

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Parkinson's disease is diagnosed by history and physical examination and there are no laboratory investigations available to aid the diagnosis of Parkinson's disease. Confirmation of diagnosis of Parkinson's disease thus remains a difficulty. This book brings forth an update of most recent developments made in terms of biomarkers and various imaging techniques with potential use for diagnosing Parkinson's disease. A detailed discussion about the differential diagnosis of Parkinson's disease also follows as Parkinson's disease may be difficult to differentiate from other mimicking conditions at times. As Parkinson's disease affects many systems of human body, a multimodality treatment of this condition is necessary to improve the quality of life of patients. This book provides detailed information on the currently available variety of treatments for Parkinson's disease including pharmacotherapy, physical therapy and surgical treatments of Parkinson's disease. Postoperative care of patients of Parkinson's disease has also been discussed in an organized manner in this text. Clinicians dealing with day to day problems caused by Parkinson's disease as well as other healthcare workers can use beneficial treatment outlines provided in this book.

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