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Cerebrospinal Fluid Biomarkers for Neurodegenerative Disorders

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Abstract

Neurodegenerative diseases are one of the major world causes of morbidity and mortality, and giving the dramatic raise in life expectancy, they are reaching epidemic proportions. These disorders form a heterogeneous group, ranging from multi-factorial dementias to rare monogenic inherited proteopathies, but they all are progressive and so far lethal, since there are no disease-modifying therapies presently available. Therefore, major research efforts are in progress for developing effective therapies, but in order to achieve this goal there is an imperative need of consistent tools for diagnosis, prognosis and monitoring drug effects and efficacy. Biomarkers have the potential to respond to all these requirements and its research is a rapidly advancing field, supported by some cases of success for other diseases, in different fields like oncology and cardiology. Pathological alterations in the brain or central nervous system could be monitored by analysis of cerebrospinal fluid and several biomarkers in this fluid have been proposed. However, almost none have reached validation and for that reason they are still not used in clinical routine. Several problems regarding lack of longitudinal studies or reproducibility between reports are still waiting to be solved. In a near future this could happen by more intensive collaboration between research centers, industry and government in different countries, in joint initiatives. This review summarizes the most relevant CSF biomarker candidates for Alzheimer's and Parkinson's disease, Amyotrophic lateral sclerosis, Huntington's and Machado Joseph disease. It also briefly passes through biomarker definitions and concepts, beyond the current limitations in this investigation area.

Contents

1. Introduction

Given the dramatic raise in life expectancy in the last century that is leading to rapidly aging populations across the world, the incidence and prevalence of neurodegenerative disorders is steadily increasing, reaching epidemic proportions. In fact, epidemiologic studies suggest that prevalence rates could double every 5 years after age 65 (Montine *et al.*, 2009). For dementia only, previsions are that it will double every 20 years during the first half of this century, increasing from approximately 35 million in 2010 to almost 120 million in 2050 (The Alzheimer's Study Group Report, 2008). These diseases are major causes of morbidity and mortality and have an enormous economic and social impact not only in patients and their families, but also in healthcare systems globally (Trojanowski *et al.*, 2011). This scenario justifies the major research efforts seen nowadays not only for effective therapies but also for the search of etiologies, pathogenic mechanisms and biomarkers that altogether can contribute to reducing the burden of such disorders.

Neurodegenerative diseases are generally defined as hereditary and sporadic conditions which are characterized by progressive loss of functions of the nervous system, often associated with atrophy of the affected central or peripheral structures (Mattsson, 2011). Another common feature that appears to be involved is the aggregation of different misfolded proteins, the reason for they are often called proteopathies. Despite the fact that they form a heterogeneous group, they all are progressive and lethal, since there is neither cure nor disease-modifying therapies currently available.

The most common symptoms are cognitive impairment and dementia, but movement disorders are also frequent. Thus, the conditions range from dementia caused by Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD), dementia with Lewy bodies (DLB), among others, to diseases leading mainly to motor impairment like Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). In addition to those multi-factorial disorders, some of these are also monogenicaly inherited, such as polyglutamine diseases, caused by the expansion of a CAG repeat encoding glutamine within the open reading frame of different genes, comprising Huntington's disease (HD) or Machado Joseph disease (MJD), to name a few. Additionally, some of these disorders may occur concomitantly and some overlap pathologically or clinically (Shaw *et al.*, 2007).

Despite the intensive research in the area and the urgent need of disease-modifying therapies, several problems remain to be solved in order to successfully achieve this goal. Usually, neurodegenerative diseases follow a slowly chronic progressive course and the first

symptoms appear only when the degenerative process has progressed for a long time (Noelker *et al.*, 2011). Moreover, the diagnosis of the majority of these diseases is based, so far, on clinical signs (confirmed by post-mortem examination of brain histology), that become apparent when there is already irreversible brain damage and the disease-modifying potential is lost (Garcia-Alloza *et al.*, 2009). Likewise, the inclusion on clinical trials of patients in different stages of the disease, or even misdiagnosed, not only limits the study power, adding the need of greater number of participants and time of follow-up, but also could compromise the evaluation of the drug efficacy.

Taken together, the reasons presented above illustrate the critical need of diagnosing individuals at the preclinical or asymptomatic phase and enroll them in clinical trials in order to identify therapies that could prevent or delay the decline in brain functions (Fagan *et al.*, 2012). It is also important an improved knowledge of disease mechanisms that could unravel new therapeutic targets and provide a better assessment of disease progression and clinical effects of promising new drugs. Biomarkers are critical tools for those and several other purposes, and its urgent requirement has been underlined on a recent publication of the US FDA's Critical Path Opportunities Report (National Institute of Mental Health, 2011).

In this review we focus on a few neurodegenerative disorders, namely Alzheimer's and Parkinson's disease, ALS and two polyglutamine diseases, Huntington's and Machado Joseph's. For each one we detail biochemical markers in the cerebrospinal fluid (CSF). The CSF is in direct contact with the CNS, and this close proximity with the affected areas by neurodegenerative diseases make it an optimal fluid for measurements, able to reflect the brain metabolism and biochemical state in health and pathology (Zetterberg *et al.*, 2006).

2. Biomarkers

The identification of specific biomarkers for neurodegenerative diseases is one of the main goals of the current clinical research mainly because they are critical for differential diagnosis between related and clinically similar pathologies, for assessment of disease-modifying drugs for which is imperative an early diagnosis and to follow disease progression that allows a better patients enrolment and objective evaluation of drug effects in clinical trials (Morgan *et al.*, 2010).

2.1. Definitions

According to the Biomarkers Definitions Working Group, a biomarker is a "characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Biomarkers Definitions Working Group, 2010). Frequently, they are classified in prognostic, diagnostic or theragnostic biomarkers, based on what they measure.

A surrogate marker is defined as a validated substitute of a clinical outcome and is expected to predict the effect of therapy (Katz, 2004). Surrogate endpoints are a subgroup of biomarkers, but given the restrictive requirements for a biomarker to be considered a surrogate marker, only a few achieve this status (Prentice, 1989).

2.2. Characteristics of an ideal biomarker

There are several requirements for a parameter to be considered a biomarker, namely validity, performance and generalizability (Constantinescu *et al.*, 2013). In order to meet the first requirement, there must be a solid correlation between the biomarker and the disease for which it is suggested. The biomarker performance answers questions related to reliability and reproducibility, as well as to the ability to differentiate between individuals affected and non-affected. It also relates with some characteristics like safety, tolerability, simplicity and low cost. Finally, the generalizability reports to the capability of maintaining a good performance not only in different patients with different age, gender, disease stage and other variables, but also in different studies performed by different groups and research or medical centers (Brooks *et al.*, 2003; Marek *et al.*, 2008).

In other words, an ideal biomarker should be sensitive, specific, reproducible, closely related with disease pathological mechanisms, easy to measure and with reduced costs,

noninvasive and thoroughly validated. Its sensitivity and specificity should be greater than 80% (van Dijk KD *et al.*, 2010).

2.3. The need for biomarkers in neurodegenerative disorders

Biomarkers can be useful for diagnostic, prognostic or drug development and for most of neurodegenerative diseases they are equally important for all of these applications, with the potential for solving many limiting issues. In fact, there are no disease modifying-therapies for these disorders so far and the lack of biomarkers is presented as one of the main reasons for that absence (Olanow *et al.*, 2008). As we pointed before, most of the patients are identified only when they present clinical symptoms, and the degeneration has already progressed so far that it may be difficult for any therapy to be effective except a symptomatic one. Also, even if patients could be identified sooner, the time frame and the number of patients in clinical trials required to see a real clinical outcome would present serious limitations, besides the difficulties presented by the lack of a reliable assessment of that outcome (Ravina *et al.,* 2003, Kieburtz *et al*., 2007).

In a more detailed way, the problems that could be solved by finding appropriate biomarkers include achievement of a differential diagnostic, establishment of time of disease onset and progression and assessment of therapy effects (Constantinescu *et al.,* 2013). In neurodegenerative disorders, a differential diagnostic could be difficult during early phases and is not uncommon to mix patients with different diseases, which may lead to negative or inconclusive results in clinical trials. A diagnostic biomarker that could point to the right diagnosis would decrease the cost, time and effort and increase the probability of success. It could also help stratifying patients with different responses to a given therapy (Marek *et al.*, 2008). As important as a correct diagnosis is an early one, since these diseases are asymptomatic for several years and even efficacious therapies may be powerless if given when neuron loss has gone too far. A biomarker able to detect the disease onset or in early phases may allow those therapies to be effective, stopping or delaying the progression of disease (Stern *et al.,* 2012). Likewise, there is still no valid way to assess the impact and benefit degree of a therapeutic intervention. Theragnostic biomarkers, i.e. those able to identify and monitor the effect of drugs, could benefit not only therapy research but also have the potential to be used as surrogate markers in clinical trials. Furthermore, biomarkers could also be useful in deciphering pathological and etiological mechanisms of such complex diseases, a knowledge helpful for design and research of new therapeutic strategies (Constantinescu *et al.,* 2013).

2.4. Biomarker modalities used in neurodegenerative diseases

For neurodegenerative diseases, as for many others, the research for biomarkers, mainly for diagnostic and prognostic purposes, could be done in body fluids or by means of imaging techniques, in addition to several clinical markers already used in clinical practice (Marek *et al*., 2008).

Many different imaging modalities are becoming widely used, particularly those based on magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), ultra-sounds and positron emission tomography (PET). This last technique is often used with different marker compounds like fluorodeoxyglucose (FDG) or amyloid ligands such as Pittsburgh compound B (PIB) and could allow correlations with biochemical markers concentration (Nordberg *et al*., 2009). One example is the inverse correlation between CSF concentrations of $A\beta_{42}$ and PIB binding, both pointing to brain amyloid burden (Fagan *et al*., 2009). Thus, it is likely helpful combining different biomarker modalities in order to increase diagnostic or prognostic accuracy (Vemuri *et al*., 2009).

Different body fluids or tissues (e.g., CSF, blood, urine, and brain tissue) could be analyzed for discovery of biochemical markers, either genetic or proteic. This research could be done in a targeted way, investigating defined compounds, usually related with the disease pathophysiology, or could be untargeted, where the researchers investigate a large amount of components in patients and controls samples. Nowadays, this kind of search is possible due to several "omics" techniques, such as genomics (genome analysis), transcriptomics (transcriptome or gene expression analysis), proteomics (proteome analysis) and metabolomics (metabolome or small-molecule metabolites analysis) (Constantinescu *et al.* 2013).

Until now, the CSF markers are probably the best studied, presenting the most promising and reproducible results. While blood or urine-based assays are desirable given its safety, tolerability and simplicity, the results are not easily reproducible or consistent. This review will focus on CSF biomarkers in neurodegenerative disorders. Blood or other body fluid markers are reviewd elsewhere (Kolarcik *et* al., 2006; Sheta *et* al., 2006; Goldknopf *et al*., 2009; Borovecki *et al*., 2010; Thambisetty *et* al., 2010; Noelker *et al*., 2011), as well as neuroimaging markers (Bohanna *et* al., 2008; Mori *et* al., 2012; Rocha *et al*., 2012; Seibyl *et* al., 2012; Weiner *et al*., 2012).

2.5. Stages of fluid biomarkers development

Generally, there are several stages in the discovery and development of new biomarkers (Rifai *et al.*, 2006). It usually begins with a discovery phase, where an initial association is made. A small number of well-characterized samples could be compared in an unbiased way for a high number of analytes or for a specific parameter that is already suggested as a possible biomarker. The candidates are then confirmed or discarded in the qualification phase, after being studied by other analytical methods and possibly in different samples. The specificity of putative biomarkers is then examined in the verification phase. In this stage a large number of samples are analyzed and assessed for variation caused by genetic, biological and environmental factors. Finally the validation phase takes place, done only on the few candidates that performed well in the previous phases (Figure 1). Several thousands of samples are then investigated for biomarker sensitivity, specificity and reproducibility, as well as its standardization potential, before further evaluation and use in clinical routine (Kroksveen *at al.*, 2011).

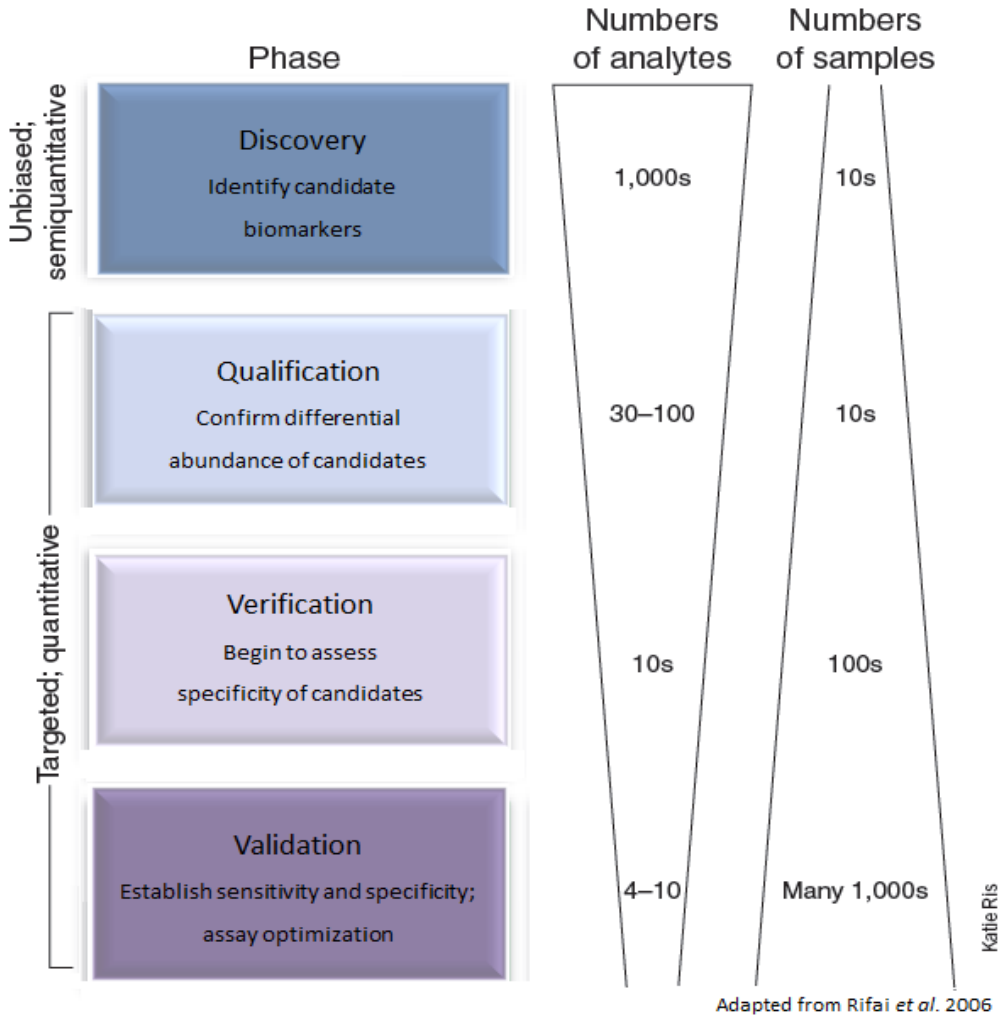


Figure 1. Stages in the development of novel biomarker candidates.

2.6. Challenges in biomarker discovery for neurodegeneration

There are several obstacles to the development of biomarkers for neurodegenerative diseases (Fagan *et al.*, 2010; Constantinescu *et al.*, 2013). First, the complexity of such disorders, with heterogeneous clinical presentations and progression, as well as a multitude of potential etiologies, raises the hypothesis that a single biomarker could not be sufficient to cover all the aspects of disease. Second, the patient classification is subjective, since criteria for clinical diagnostic may have different interpretations and change over time, lacking accuracy, particularly at early stages of the disease. Confirming the diagnosis and at the same time the value of a biomarker, is almost unrealistic, since it requires a postmortem brain examination and these diseases progress at a slow rate. Third, due to the difficulties explained above for identifying patients in preclinical stages, it is highly probable that some of them may be included in control groups, thus affecting the results of biomarkers performance. Fourth, the patient sample size is usually limited and not corrected for the impact of variables such as age, gender, and APOE genotype, which restrict the generalizability of results. Fifth, biochemical markers concentrations vary considerably between studies, probably due to analytical factors related with sample collection and handling, or differences in protocols and kits used for measurements (Bjerke *et al.*, 2010; Mattsson *et al.*, 2010), limiting the reproducibility and the direct comparison of results and raising the need for methods harmonization. In order to overcome these issues, there are some joint programs involving different countries and research centers, with the common goal of finding causes, cures and developing accurate biomarkers. One of these initiatives is the EU Joint Programme for Neurodegenerative Disease Research (JNPD), already involving 21 countries and having one programme in particular dedicated to biomarkers information and harmonization, the BIOMARKAPD. This program offers details about standardization in biomarker measurements, samples collection and results interpretation (EU JPND Research, 2011).

3. Alzheimer's disease

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease, affecting approximately 10.6 million people in USA and Europe and this number is estimated to rise to 15.4 million in 2030 (Alzheimer's Association, 2011). In 2011, the cost of care in the USA alone was almost US$183 billion and the projected costs for 2050 are over US$1.1 trillion if an effective disease-modifying therapy remains elusive (Brookmeyer *et al.*, 2011).

Although phenotypically indistinguishable, the disease is generally classified according to the age of onset and presence of genetic heterogeneity, in late and early onset, typically corresponding to sporadic and familial forms, respectively. The vast majority of cases (more than 90%) are sporadic, diagnosed after 65 years of age, with no known genetic cause associated (Tandon *et al.*, 2000).

3.1. Clinical presentation and diagnosis

Most frequently, the first symptom in patients suffering from AD is the difficulty to remember new information, caused by neuronal loss in the brain regions responsible for memory, specifically the cerebral cortex and hippocampus (Selkoe, 2001). As the brain damage progress patients could experience more severe memory loss, disorientation, inability to perform simple daily tasks, confusion, alterations of language and learning, decreased judgment, changes in mood and personality and an extensive decline in general cognitive function (Tanzi *et al.*, 2005; Alzheimer's Association, 2013).

The definitive diagnosis is only possible postmortem, by a histological brain analysis. The clinical ante-mortem diagnosis is currently based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) or on criteria from the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann *et al.*, 1984). Some of the principles in these documents include the development of memory impairment and one or more cognitive disturbances, which should exhibit gradual onset and cause impairment in daily living. However, these symptoms are very similar to other causes of dementia and they should be excluded, when possible, by means of medical and family history, physical and neurologic evaluation, and laboratory and neuroimaging tests (Hooper *et al.*, 2008). Despite all these efforts, the diagnostic success rate is still very low, mainly at early stages, where symptoms are still subtle and do not interfere with daily activities, meeting the criteria for mild cognitive impairment (MCI) (Peterson *et al.*, 1999). These patients show deficits on

cognitive tests when compared with age-matched controls, and studies suggest that it could be a stage between normal aging and dementia, frequently seen as a prodromal phase of AD (Grundman *et al.*, 2004). Actually, the risk for patients with MCI to develop AD almost tripled compared to healthy controls, during a follow-up period of 5 years, but since MCI is a heterogeneous disorder, it may also progress to other dementias or only to the cognitive decline seen in normal aging (Rosén *et al*., 2013).

More recently, in face of the difficulties described above and the advances in imaging techniques (PET scan with Pittsburgh compound) and the validation of some core biomarkers (amyloid beta and tau protein) in CSF, the National Institute on Aging and Alzheimer's Association workgroups have recommended the inclusion of these techniques and parameters on diagnostic guidelines (Albert *et* al., 2011; McKhann *et al*., 2011).

3.2. Pathological features

The fundamental brain pathology in Alzheimer's disease is characterized by extracellular senile plaques and intracellular neurofibrillary tangles. The amyloid or senile plaques are dense, mostly insoluble deposits of β-amyloid (Aβ) peptide outside neurons. These peptides are generated from two consecutive proteolytic cleavages of a larger protein called amyloid precursor protein (APP) by two enzymes: β-secretase (BACE-1 for *β-site APP cleaving enzyme*) and γ-secretase. The neurofibrillary tangles are insoluble twisted fibers of hyperphosphorilated tau protein that build up inside the nerve cell (Pastorino *et al*., 2006). According to the amyloid cascade theory, the deposition of Aβ is believed to be one of the central events in AD pathogenesis, which is also supported by familial cases of the disease caused by mutations in this peptide precursor or in the enzymes responsible for its cleavage. The Aβ peptide (particularly the isoform with 42 amino acids, $A\beta_{42}$) seems to have an initiating role for other pathological features, namely astrocyte and glial activation that in turn leads to production of inflammatory mediators. The neuroinflammation and oxidative stress are responsible for the activation of several kinases and phosphatases, involved in tau hyperphosphorylation and consequent development of neurofibrillary tangles. The degenerative process spreads across neurons, disrupting axonal transport, damaging synapses and depleting neurotransmitters (particularly cholinergic), finally culminating in neuronal cell death, the ultimate responsible for dementia (Hardy, 2002).

Notwithstanding the role of Aβ for the neurodegenerative process, several studies report a strong correlation between tangles and severity of dementia, but not for levels of amyloid peptides or senile plaques (Bierer *et al.*, 1995; Nagy *et al.*, 1995).

3.3. Most promising biomarkers for AD in CSF

Reflecting their role in Alzheimer's disease pathogenesis, the most useful biomarkers so far are levels of $A\beta_{42}$, total and hyperphosphorilated tau protein (t-Tau and p-Tau, respectively) and their ratios. These proteins in the cerebrospinal fluid are the first validated and well established biomarkers of neurodegenerative diseases, and have been extensively studied by several groups and researchers (Fagan *et al*., 2012). Their findings are summarized in Table 1.

Table 1. Validated CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
Markers related with pathophysiology				
$A\beta_{42}$	Poorly understood	↓	37/32	Motter *et al.* 1995
		↓	24/25	Ida *et al.* 1996
		↓	20/34	Tamaoka *et al.* 1997
		↓	82/60	Galasko *et al.* 1998
		↓	93/143	Kanai *et al.* 1998
		↓	55/34	Shoji et al., 1998
		↓	53/21	Andreasen *et al.* 1999a
		↓	16/15	Andreasen *et al.* 1999b
		↓	150/100	Hulstaert *et al.* 1999
		↑	80/24	Jensen *et al.* 1999
		↓	23/13	Fukuyama *et al.* 2000
		↓	24/19	Kanemaru *et al.* 2000
		↓	36/29	Mehta *et al.* 2000
		↓	14/20	Otto *et al.* 2000
		↓	75/35	Riemenschneider *et al.* 2000
		↓	60/32	Sjogren *et al.* 2000
		↓	39/12	Vanderstichele *et al.* 2000
		↓	163/18	Andreasen *et al.* 2001
		↓	38/47	Kapaki *et al.* 2001
		↓	19/10	Montine *et al.* 2001
		↓	27/70	Rösler *et al.* 2001
		↓	32/10	Csernansky *et al.* 2002
		↓	20/20	Mulder *et al.* 2002
		↓	73/27	Nagga *et al.* 2002
		↓	19/17	Sjögren et al. 2002
		↓	44/32	Andreasen *et al.* 2003
		↓	106/69	Clark *et al.* 2003
		↓	33/46	Gómez-Tortosa *et al.* 2003
$A\beta_{42}$	Poorly understood	↓	49/49	Kapaki *et al.* 2003
		↓	27/35	Skoog *et al.* 2003
		↓	131/72	Sunderland *et al.* 2003
		↓	145/10	Hampel *et al.* 2004b
		↓	22/35	Lewczuk *et al.* 2004
		↓	17/13	Grossman *et al.* 2005
		↓	46/78	Herukka *et al.* 2005

Table 1 *(continued)*. Validated CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
$A\beta_{42}$	Poorly understood	↓	39/35	Jia *et al.* 2005
		↓	23/27	Blasko *et al.* 2006
		↓	6/18	Fagan *et al.* 2006
		↓	49/90	Fagan *et al.* 2007
		↓	79/60	Herukka *et al.* 2007
		↓	100/100	Engelborghs *et al.* 2008
		↓	22/21	Brys *et al.* 2009
		↓	35/29	Hansson *et al.* 2009
		↓	30/30	Bjerke *et al.* 2011
		↓	98/211	Tarawneh *et al.* 2011
		↓	88/155	Lewczuk *et al.* 2012
		↓	60/28	Parnetti *et al.* 2012
		↓	61/40	Luo *et al.* 2013
*t*Tau	Microtubule stabilization	↑	27/51	Vandermeeren *et al.* 1993
		↑	70/115	Arai *et al.* 1995
		↑	44/31	Blennow *et al.* 1995b
		↑	19/18	Hock *et al.* 1995
		↑	82/22	Jensen *et al.* 1995
		↑	14/36	Mori *et al.* 1995
		↑	37/32	Motter *et al.* 1995
		↑	24/14	Munroe *et al.* 1995
		↑	26/35	Skoog *et al.* 1995
		↑	23/23	Tato *et al.* 1995
		↑	71/110	Vigo-Pelfrey *et al.* 1995
		↑	18/9	Blomberg *et al.* 1996
		↑	22/19	Riemenschneider *et al.* 1996
		↑	16/26	Rösler *et al.* 1996
		↑	91/77	Arai *et al.* 1997a
		↑	17/15	Arai *et al.* 1997b
		↑	36/14	Galasko *et al.* 1997
		↑	19/12	Golombowski *et al.* 1997
		↑	43/18	Andreasen *et al.* 1998
		↑	69/17	Arai *et al.* 1998
		↑	82/60	Galasko *et al.* 1998
		↑	93/143	Kanai *et al.* 1998
		↑	40/36	Kurz *et al.* 1998
		↑	29/23	Mecocci *et al.* 1998
*t*Tau	Microtubule stabilization	↑	163/65	Nishimura *et al.* 1998
		↑	55/34	Shoji *et al.* 1998
		↑	81/33	Tapiola *et al.* 1998
		↑	16/15	Andreasen *et al.* 1999b
		↑	38/28	Buerger *et al.* 1999
		↑	25/19	Hampel *et al.* 1999
		↑	150/100	Hulstaert *et al.* 1999
		↑	17/23	Green *et al.* 1999
		↑	36/20	Ishiguro *et al.* 1999
		↑	83/88	Molina *et al.* 1999

Table 1 *(continued)*. Validated CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
*t*Tau	Microtubule stabilization	↑	36/23	Morikawa *et al.* 1999
		↑	34/25	Tarkowski *et al.* 1999
		↑	35/16	Kahle *et al.* 2000
		↑	24/19	Kanemaru *et al.* 2000
		↑	60/32	Sjogren *et al.* 2000a
		↑	42/18	Sjogren *et al.* 2000b
		↑	163/18	Andreasen *et al.* 2001
		↑	17/12	Hampel *et al.* 2001
		↑	236/95	Itoh *et al.* 2001
		↑	38/47	Kapaki *et al.* 2001
		↑	19/10	Montine *et al.* 2001
		↑	80/40	Parnetti *et al.* 2001
		↑	27/70	Rösler *et al.* 2001
		↑	60/17	Sjogren *et al.* 2001a
		↑	47/12	Sjogren *et al.* 2001b
		↑	32/10	Csernansky *et al.* 2002
		↑	52/56	Hu *et al.* 2002b
		↑	20/20	Mulder *et al.* 2002
		↑	73/27	Nagga *et al.* 2002
		↑	19/17	Sjögren *et al.* 2002
		↑	366/181	Shoji *et al.* 2002
		↑	44/32	Andreasen *et al.* 2003
		↑	106/69	Clark *et al.* 2003
		↑	33/46	Gómez-Tortosa *et al.* 2003
		↑	49/49	Kapaki *et al.* 2003
		↑	25/16	Schönknecht *et al.* 2003
		↑	131/72	Sunderland *et al.* 2003
		↑	145/10	Hampel *et al.* 2004b
		↑	22/35	Lewczuk *et al.* 2004
		↑	17/13	Grossman *et al.* 2005
		↑	46/78	Herukka *et al.* 2005
		↑	39/35	Jia *et al.* 2005
		↑	23/27	Blasko *et al.* 2006
		↑	49/90	Fagan *et al.* 2007
*p*Tau	Microtubule stabilization	↑	79/60	Herukka *et al.* 2007
		↑	100/100	Engelborghs *et al.* 2008
		↑	22/21	Brys *et al.* 2009
		↑	55/130	van Eijk *et al.* 2010
		↑	30/30	Bjerke *et al.* 2011
		↑	98/211	Tarawneh *et al.* 2011
		↑	60/28	Parnetti *et al.* 2012
		↑	61/40	Luo *et al.* 2013
		↑	44/31	Blennow *et al.* 1995b
		↑	36/20	Ishiguro *et al.* 1999
		↑	27/31	Kohnken *et al.* 2000
		↑	17/12	Hampel *et al.* 2001
		↑	236/95	Itoh *et al.* 2001

Table 1 *(continued)*. Validated CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
*p*Tau	Microtubule stabilization	↑	80/40	Parnetti *et al.* 2001
		↑	60/17	Sjogren *et al.* 2001
		↑	82/21	Buerger *et al.* 2002
		↑	52/56	Hu *et al.* 2002b
		↑	73/27	Nagga *et al.* 2002
		↑	19/17	Sjögren et al. 2002
		↑	44/32	Andreasen *et al.* 2003
		↑	81/21	Buerger *et al.* 2003
		↑	25/16	Schönknecht *et al.* 2003
		↑	108/45	Hampel *et al.* 2004a
		↑	17/13	Grossman *et al.* 2005
		↑	46/78	Herukka *et al.* 2005
		↑	39/35	Jia *et al.* 2005
		↑	23/27	Blasko *et al.* 2006
		↑	49/90	Fagan *et al.* 2007
		↑	79/60	Herukka *et al.* 2007
		↑	100/100	Engelborghs *et al.* 2008
		↑	22/21	Brys *et al.* 2009
		↑	30/30	Bjerke *et al.* 2011
		↑	88/155	Lewczuk *et al.* 2012
		↑	60/28	Parnetti *et al.* 2012
		↑	61/40	Luo *et al.* 2013

↑ increased; ↓ decreased; ↔ no significant alterations; Control refers to healthy subjects.

Aβ42: Beta amyloid; *t-Tau*: Total tau protein; *p-Tau*: Phosphorylated tau protein.

In a general way, increased levels of tau protein and decreased levels of $A\beta_{42}$ are found in CSF of AD patients, as compare to healthy, non-demented controls. Only one study reported a significant increase of $A\beta_{42}$ in CSF of patients in early and mid-stages of AD, yet declining with disease progression (Jensen *et al.*, 1999), which may be explained by methodological factors. Low levels of Aβ42 are associated with amyloid deposition in plaques (Fagan et al., 2006), while elevated tau levels, total or hyperphosphorilated, are expected as a result from tissue damage and the development of neurofibrillary tangles (Buerger et al., 2006).These markers not only have a sensitivity and specificity greater than 80% for diagnosing AD, but are also able to identify the disease at early stages, namely in patients with mild cognitive impairment (MCI), predicting the development of Alzheimer's (Riemenschneider *et* al., 2002; Herukka *et* al., 2005, Hansson *et al.*, 2006; Hansson *et al.*, 2007; Herukka *et* al., 2007; Mattsson *et* al., 2012; Palmqvist *et al.*, 2012; Parnetti *et al.*, 2012; Tabaraud *et al.*, 2012).

3.4. Recent candidate biomarkers in CSF

Aiming an increase in diagnostic accuracy and reducing variability between studies, numerous other biomarker candidates are being pursued, that can identify mixed pathologies and additional processes involved in AD. In Figure 2 are represented some of the most relevant complementary candidate markers, reflecting more general neurodegenerative mechanisms, like neuroinflammation and synaptic dysfunction and loss, as well as some others whose involvement in Alzheimer's disease is not well understood so far (Fagan *et al.*, 2012).

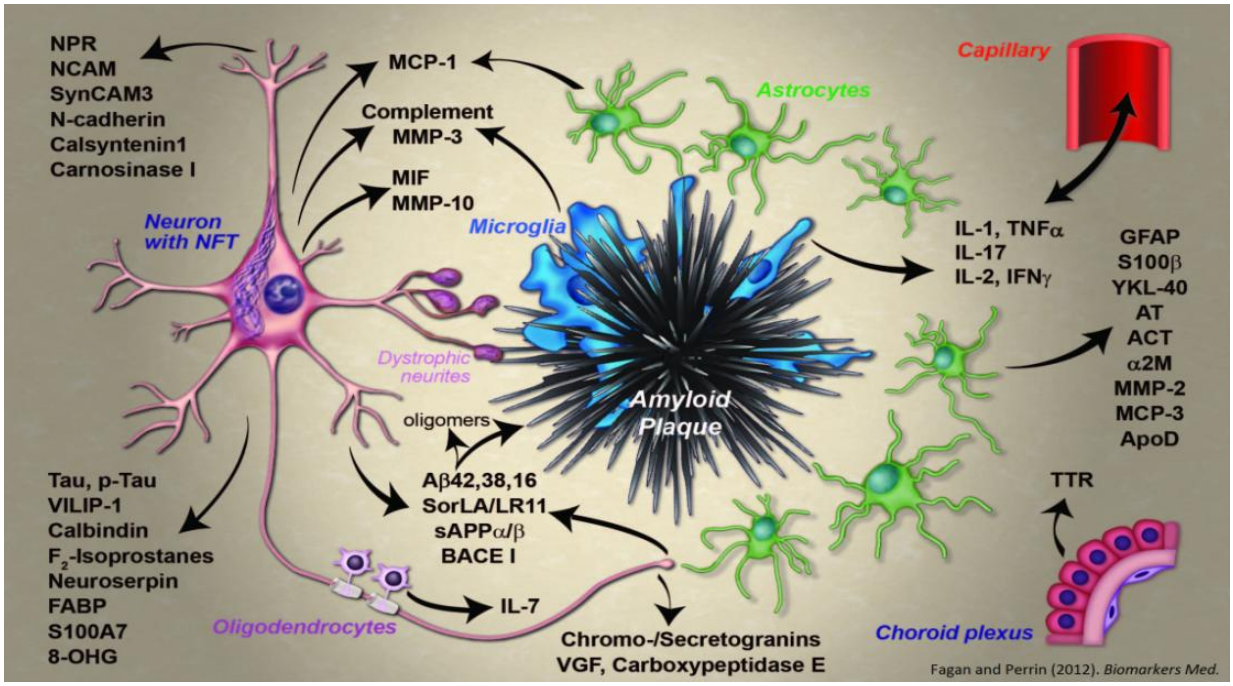


Figure 2. Schematic representation of the origin of CSF biomarkers in AD (Fagan *et al.*, 2012). In addition to core biomarkers, some neuronal proteins as well as neurotrophic and growth factors, generally decline in AD, perhaps reflecting synapse and neuronal loss. On the other hand, neuroinflammatory mediators and products of oxidative damage are usually elevated. (Molecules name abbreviations are detailed in Table 2).

The most important findings for those markers are summarized in Table 2. Only potential biomarkers with at least one study reporting an increased or decreased value are presented.

Table 2. Candidate CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
Markers related with axonal degeneration				
NfH	Axonal structure	↑	52/66	Hu *et al.* 2002a
	protein	↑	109/58	Brettschneider *et al.* 2006d

Table 2 *(continued)*. Candidate CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
NfH	Axonal structure protein	↑	55/130	van Eijk *et al.* 2010
		↔	68/24	Kester *et al.* 2012
NfL	Axonal structure protein	↑	42/18	Sjogren *et al.* 2000b
		↑	52/66	Hu *et al.* 2002a
		↑	20/25	Pijnenburg *et al.* 2007
		↑	55/130	van Eijk *et al.* 2010
		↑	30/30	Bjerke *et al.* 2011
		↔	68/24	Kester *et al.* 2012
TG	Protein cross-linking	↑	33/33	Bonelli *et al.* 2002
sAPP	Neurotrophic factor	↓	45/26	Peskind *et al.* 1997
		↔	14/15	Hock *et al.* 1998
		↓	13/13	Sennvik *et al.* 2000
		↑	47/12	Sjögren *et al.* 2001b
		↓	32/10	Csernansky *et al.* 2002
		↓	25/16	Wu *et al.* 2011
sAPPβ	Neurite outgrowth	↔	13/13	Sennvik *et al.* 2000
		↔	81/43	Olsson *et al.* 2003
		↑	87/33	Zetterberg *et al.* 2008
		↑	69/48	Lewczuk *et al.* 2010
		↓	25/16	Wu *et al.* 2011
		↑	88/155	Lewczuk *et al.* 2012
		↔	75/65	Rosén *et al.* 2012
		↔	43/44	Brinkmalm *et al.* 2013
sAPPα	Neurotrophic factor	↓	13/13	Sennvik *et al.* 2000
		↓	33/22	Colciaghi *et al.* 2002
		↔	81/43	Olsson *et al.* 2003
		↑	87/33	Zetterberg *et al.* 2008
		↑	69/48	Lewczuk *et al.* 2010
		↓	25/16	Wu *et al.* 2011
		↑	88/155	Lewczuk *et al.* 2012
		↔	75/65	Rosén *et al.* 2012
		↔	43/44	Brinkmalm *et al.* 2013
GFAP	Cytoskeletal protein	↑	37/39	Wallin *et al.* 1996
		↑	27/26	Fukuyama *et al.* 2001
		↑	18/14	Jesse *et al.* 2009
		↑	55/130	van Eijk *et al.* 2010
Markers related with inflammation and immune response				
IL-1 beta	Immune response	↔	13/15	Martinez *et al.* 1993b
		↔	40/42	Pirttila *et al.* 1994
		↑	11/12	Blum-Degen *et al.*1995
		↔	8/9	Lanzrein *et al.* 1998
		↔	42/20	Engelborghs *et al.* 1999
		↔	34/25	Tarkowski *et al.* 1999
		↔	10/10	Martínez *et al.* 2000
		↔	33/46	Gómez-Tortosa *et al.*
		↔	20/21	Richartz *et al.* 2005
sIL-1R	Immune response	↑	12/13	Garlind *et al.* 1999

Table 2 *(continued)*. Candidate CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
IL-6	Immune response	↑	11/12	Blum-Degen *et al.*1995
		↓	12/7	Yamada *et al.* 1995
		↔	25/19	Hampel *et al.* 1997
		↔	17/18	März *et al.* 1997
		↔	8/9	Lanzrein *et al.* 1998
		↔	42/20	Engelborghs *et al.* 1999
		↔	12/13	Garlind *et al.* 1999
		↔	25/19	Hampel *et al.* 1999
		↔	34/25	Tarkowski *et al.* 1999
		↑	10/10	Martínez *et al.* 2000
		↑	27/70	Rösler *et al.* 2001
		↑	33/46	Gómez-Tortosa *et al.*
		↑	39/35	Jia *et al.* 2005
		↔	20/21	Richartz *et al.* 2005
IL-6	Immune response	↔	43/30	Galimberti *et al.* 2008
		↔	31/19	Popp *et al.* 2009
sIL-6R	Immune response	↔	17/18	März *et al.* 1997
		↓	41/41	Hampel *et al.* 1998
		↓	25/19	Hampel *et al.* 1999
		↑	58/25	Bagli *et al.* 2003
Gp130	Cytokine receptor	↔	17/18	März *et al.* 1997
		↓	25/19	Hampel *et al.* 1999
IL-7	Immune response	↓	66/33	Hu *et al.* 2010
		↓	91/242	Craig-Schapiro *et al.*
IL-11	Immune response	↑	43/30	Galimberti *et al.* 2008
TRAIL-R3	Immune response	↑	66/33	Hu *et al.* 2010
		↑	91/242	Craig-Schapiro *et al.*
MIF	Inflammatory response	↑	31/19	Popp *et al.* 2009
		↑	91/242	Craig-Schapiro *et al.*
Isoprostanes	Inflammatory mediators	↑	11/11	Montine *et al.* 1998
		↑	4/3	Roberts *et al.* 1998
		↑	7/7	Montine *et al.* 1999b
		↑	14/10	Praticò *et al.* 2000
Isoprostanes	Inflammatory mediators	↑	19/10	Montine *et al.* 2001
		↑	28/18	Praticò *et al.* 2002
		↑	17/13	Grossman *et al.* 2005
		↑	6/11	de Leon *et al.* 2007
		↑	22/21	Brys *et al.* 2009
		↔	68/24	Kester *et al.* 2012
		↑	63/20	Duits *et al.* 2013
PG	Inflammatory mediators	↑	7/7	Montine *et al.* 1999b
		↓	7/7	Puchades *et al.* 2003
		↓	11/8	Korolainen *et al.* 2007
Pentraxin	Immune response	↑	10/10	Abdi *et al.* 2006
		↑	52/44	Finehout *et al.* 2007
		↑	3/3	Yin *et al.* 2009

Table 2 *(continued)*. Candidate CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
C3	Inflammatory response	↓	82/21	Buerger *et al.* 2002
		↔	9/9	Finehout *et al.* 2005
		↑	52/44	Finehout *et al.* 2007
		↑	113/28	Simonsen *et al.* 2007
		↑	125/100	Simonsen *et al.* 2008
		↑	66/33	Hu *et al.* 2010
		↑	50/137	Wang *et al.* 2011
C4	Inflammatory response	↑	9/9	Finehout *et al.* 2005
		↑	10/10	Abdi *et al.* 2006
		↑	113/28	Simonsen *et al.* 2007
		↓	3/3	Yin *et al.* 2009
		↑	24/24	Perrin *et al.* 2011
Factor H	Inflammatory	↑	50/137	Wang *et al.* 2011
MCP-1	Inflammatory response	↑	23/27	Blasko *et al.* 2006
		↔	11/13	Choi *et al.* 2008
		↑	91/242	Craig-Schapiro *et al.*
		↑	47/30	Westin *et al.* 2012
TNF-α	Immune response	↔	8/9	Lanzrein *et al.* 1998
		↔	42/20	Engelborghs *et al.* 1999
		↔	12/13	Garlind *et al.* 1999
		↑	34/25	Tarkowski *et al.* 1999
		↑	52/25	Tarkowski *et al.* 2000
		↑	39/35	Jia *et al.* 2005
		↓	20/21	Richartz *et al.* 2005
		↔	23/27	Blasko *et al.* 2006
		↔	31/19	Popp *et al.* 2009
sTNFR	Immune response	↔	8/9	Lanzrein *et al.* 1998
		↔	34/25	Tarkowski *et al.* 1999
		↔	20/21	Richartz *et al.* 2005
		↑	137/30	Buchhave *et al.* 2010
		↑	91/242	Craig-Schapiro *et al.*
sTNFR	Immune response	↑	32/27	Jiang *et al.* 2011
Neopterin	Immune response	↔	42/20	Engelborghs *et al.* 1999
		↔	24/16	Milstien *et al.* 1994
Markers related with neuroprotection				
GAP-43	Axonal growth	↑	47/12	Sjogren *et al.* 2001b
TGFβ-1	Growth factor	↑	20/27	Tarkowski *et al.* 2002
		↑	20/20	Zetterberg *et al.* 2004
		↔	23/27	Blasko *et al.* 2006
		↑	30/25	Rota *et al.* 2006
PEDF	Neurotrophic factor	↑	43/43	Castaño *et al.* 2006
		↔	47/43	Roher *et al.* 2009
		↔	27/27	Abraham *et al.* 2011
VEGF	Angiogenic factor	↑	20/27	Tarkowski *et al.* 2002
		↔	23/27	Blasko *et al.* 2006
		↓	91/242	Craig-Schapiro *et al.*

Table 2 *(continued)*. Candidate CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
VEGF	Angiogenic factor	↓	69/92	Guo *et al.* 2013
VGF	Growth factor	↓	9/10	Carrette *et al.* 2003
		↓	113/28	Simonsen *et al.* 2007
		↓	125/100	Simonsen *et al.* 2008
		↓	34/17	Jahn *et al.* 2011
		↓	24/24	Perrin *et al.* 2011
Clusterin	Chaperone	↓	7/7	Puchades *et al.* 2003
		↑	12/12	Sihlbom *et al.* 2008
		↔	66/33	Hu *et al.* 2010
		↔	91/242	Craig-Schapiro *et al.*
Clusterin	Chaperone	↔	24/24	Perrin *et al.* 2011
Cystatin C	Cysteine protease inhibitor	↑	9/10	Carrette *et al.* 2003
		↑	113/28	Simonsen *et al.* 2007
		↑	125/100	Simonsen *et al.* 2008
		↓	35/29	Hansson *et al.* 2009
		↓	91/242	Craig-Schapiro *et al.*
		↓	24/24	Perrin *et al.* 2011
		↔	101/28	Sundelöf *et al.* 2012
β2microglobulin	HLA complex	↑	13/15	Martinez *et al.* 1993b
		↑	15/12	Davidsson *et al.* 2002
		↑	9/10	Carrette *et al.* 2003
		↓	7/7	Puchades *et al.* 2003
		↑	10/10	Abdi *et al.* 2006
		↑	113/28	Simonsen *et al.* 2007
		↓	125/100	Simonsen *et al.* 2008
		↓	24/24	Perrin *et al.* 2011
Markers related with oxidative stress				
HNE	Lipid peroxidation	↑	19/13	Lovell *et al.* 1997
		↑	8/6	Selley *et al.* 2002
8-OHdG	DNA oxidative damage	↑	18/7	Lovell *et al.* 2001
		↑	18/15	Abe *et al.* 2005
		↑	30/30	Isobe *et al.* 2010
3-NT	Protein nitration	↑	25/24	Tohgi *et al.* 1999a
		↑	32/18	Ahmed *et al.* 2005
SOD1	Detoxification	↓	22/41	Boll *et al.* 2008
Nitrate	NO biotransformation	↓	13/20	Kuiper *et al.* 1994b
		↔	24/16	Milstien *et al.* 1994
		↔	36/36	Navarro *et al.* 1996
		↑	22/41	Boll *et al.* 2008
Haptoglobin	Hemoglobin binding	↑	10/10	Abdi *et al.* 2006
		↓	30/30	Jung *et al.* 2008
		↓	27/27	Abraham *et al.* 2011
Transferrin	Iron binding	↑	14/25	Chapel *et al.* 1984
		↔	17/11	Loeffler *et al.* 1994
Ceruloplasmin	Copper transport	↑	17/11	Loeffler *et al.* 1994
		↔	10/10	Abdi *et al.* 2006

Table 2 *(continued)*. Candidate CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
Others				
α-Synuclein	Poorly understood	↓	66/55	Ohrfelt *et al.* 2009
		↔	26/24	Wennstrom *et al.* 2012
		↑	200/200	Korff *et al.* 2013
		↓	61/40	Luo *et al.* 2013
hFABP	Fatty acid metabolism	↑	32/25	Chiasserini *et al.* 2010
		↑	66/33	Hu *et al.* 2010
		↑	30/30	Bjerke *et al.* 2011
hFABP	Fatty acid metabolism	↑	91/242	Craig-Schapiro *et al.*
		↑	69/92	Guo *et al.* 2013
MMP-2	Protein degradation	↓	5/15	Mlekusch *et al.* 1999
		↔	31/41	Lorenzl *et al.* 2003
		↓	14/14	Horstmann *et al.* 2010
		↔	30/30	Bjerke *et al.* 2011
MMP-3	Protein degradation	↓	5/15	Mlekusch *et al.* 1999
		↑	14/14	Horstmann *et al.* 2010
		↑	38/34	Stomrud *et al.* 2010
		↔	30/30	Bjerke *et al.* 2011
MMP-9	Protein degradation	↑	31/41	Lorenzl *et al.* 2003
		↔	30/30	Adair *et al.* 2004
		↑	38/34	Stomrud *et al.* 2010
		↔	30/30	Bjerke *et al.* 2011
MMP-10	Protein degradation	↑	91/242	Craig-Schapiro *et al.*
		↑	30/30	Bjerke *et al.* 2011
PP	Pancreatic regulation	↑	66/33	Hu *et al.* 2010
		↑	91/242	Craig-Schapiro *et al.*
Resistin	Secretory factor	↑	66/33	Hu *et al.* 2010
		↑	91/242	Craig-Schapiro *et al.*
TIMP-1	MMP-1 inhibitor	↑	31/41	Lorenzl *et al.* 2003
		↓	38/34	Stomrud *et al.* 2010
		↔	30/30	Bjerke *et al.* 2011
TIMP-2	MMP-2 inhibitor	↑	31/41	Lorenzl *et al.* 2003
		↔	30/30	Bjerke *et al.* 2011
Glutamate	Excitotoxicity	↔	11/23	Smith *et al.* 1985
		↓	22/11	Basun *et al.* 1990
		↑	10/10	Pomara *et al.* 1992
		↓	13/15	Martinez *et al.* 1993a
		↑	37/32	Jiménez-Jiménez *et al.*
Transthyretin	Thyroid hormone binding	↓	40/109	Serot *et al.* 1997
		↓	20/10	Merched *et al.* 1998
		↑	15/12	Davidsson *et al.* 2002
		↓	7/7	Puchades *et al.* 2003
		↑	10/10	Abdi *et al.* 2006
		↓	43/43	Castaño *et al.* 2006
		↑	52/44	Finehout *et al.* 2007
		↓	11/8	Korolainen *et al.* 2007

Table 2 *(continued)*. Candidate CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
Transthyretin	Thyroid hormone binding	↓	23/19	Gloeckner *et al.* 2008
		↓	35/29	Hansson *et al.* 2009
		↔	47/43	Roher *et al.* 2009
Transthyretin	Thyroid hormone binding	↔	59/13	Schultz *et al.* 2010
		↓	24/24	Perrin *et al.* 2011
Gelsolin	Actin binding protein	↓	39/55	Hu *et al.* 2007
		↓	24/24	Perrin *et al.* 2011
IGF-1	Cell proliferation	↑	41/41	Salehi *et al.* 2008
		↔	32/20	Johansson *et al.* 2013
IGFBP	IGF binding protein	↑	41/41	Salehi *et al.* 2008
		↑	91/242	Craig-Schapiro *et al.*
		↔	32/20	Johansson *et al.* 2013
α1-Antitrypsin	Protease inhibitor	↔	5/7	Delamarche *et al.* 1991
		↓	7/7	Puchades *et al.* 2003
		↑	10/10	Abdi *et al.* 2006
		↑	52/44	Finehout *et al.* 2007
		↑	258/37	Nielsen *et al.* 2007
		↑	60/37	Ewers *et al.* 2008
		↓	12/12	Sihlbom *et al.* 2008
		↓	35/29	Hansson *et al.* 2009
		↑	3/3	Yin *et al.* 2009
		↑	91/242	Craig-Schapiro *et al.*
ACT	Protease inhibitor	↑	15/26	Matsubara *et al.* 1990
		↔	5/7	Delamarche *et al.* 1991
		↔	24/25	Furby *et al.* 1991
		↔	40/42	Pirttila *et al.* 1994
		↑	66/54	Harigaya *et al.* 1995
		↑	33/11	Licastro *et al.* 1995
		↔	8/9	Lanzrein *et al.* 1998
		↑	34/16	DeKosky *et al.* 2003
		↑	39/55	Hu *et al.* 2007
		↑	258/37	Nielsen *et al.* 2007
		↓	125/100	Simonsen *et al.* 2008
		↑	24/24	Perrin *et al.* 2011
Neuroserpin	Protease inhibitor	↑	258/37	Nielsen *et al.* 2007
α2Macroglobulin	Antiprotease	↑	66/33	Hu *et al.* 2010
		↑	24/24	Perrin *et al.* 2011
ZAG	Lipid mobilization	↑	39/55	Hu *et al.* 2007
		↓	47/43	Roher *et al.* 2009
Tetranectin	Plasminogen binding	↑	6/7	Wang *et al.* 2010
		↓	33/20	Vafadar *et al.* 2012
Fibrinogen	Coagulation cascade	↑	10/10	Abdi *et al.* 2006
		↑	52/44	Finehout *et al.* 2007
		↑	91/242	Craig-Schapiro *et al.*
		↑	33/20	Vafadar *et al.* 2012
ATIII	Coagulation cascade	↑	39/55	Hu *et al.* 2007
CNDP1	Carnosine hydrolysis	↓	39/55	Hu *et al.* 2007

Table 2 *(continued)*. Candidate CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
CNDP1	Carnosine hydrolysis	↑	3/3	Yin *et al.* 2009
		↓	24/24	Perrin *et al.* 2011
Osteopontin	Stress and inflammation	↑	67/69	Comi *et al.* 2010
		↑	91/242	Craig-Schapiro *et al.*
		↑	35/20	Sun *et al.* 2013
Copper	Micronutrient	↑	24/28	Basun *et al.* 1991
		↔	26/28	Molina *et al.* 1998
		↔	22/41	Boll *et al.* 2008
		↔	173/54	Gerhardsson *et al.* 2008
		↔	116/129	Bucossi *et al.* 2011
		↑	21/15	Hozumi *et al.* 2011
Orexin	Neurotransmitter	↑	26/24	Wennstrom *et al.* 2012
		↓	24/25	Fronczek *et al.* 2012
		↑	33/33	Schmidt *et al.* 2013
HVA	Dopamine metabolite	↓	15/19	Bareggi *et al.* 1982
		↔	11/32	Wood *et al.* 1982
		↑	10/15	Zubenko *et al.* 1986
		↓	22/32	Kawakatsu *et al.* 1990
HVA	Dopamine metabolite	↔	60/12	Molchan *et al.* 1991
		↓	123/57	Blennow *et al.* 1992
		↑	27/34	Hartikainen *et al.* 1992
		↓	15/14	Parnetti *et al.* 1992
		↓	60/31	Sjogren *et al.* 1998
5HIAA	Serotonin metabolite	↔	15/19	Bareggi *et al.* 1982
		↔	11/32	Wood *et al.* 1982
		↓	22/32	Kawakatsu *et al.* 1990
		↔	60/12	Molchan *et al.* 1991
		↓	123/57	Blennow *et al.* 1992
		↑	27/34	Hartikainen *et al.* 1992
		↓	15/14	Parnetti *et al.* 1992
		↓	60/31	Sjogren *et al.* 1998
MHPG	Norepinephrine metabolite	↔	11/32	Wood *et al.* 1982
		↔	60/12	Molchan *et al.* 1991
		↔	123/57	Blennow *et al.* 1992
		↔	27/34	Hartikainen *et al.* 1992
		↔	15/14	Parnetti *et al.* 1992
		↔	60/31	Sjogren *et al.* 1998
		↓	79/51	Czech *et al.* 2012
AChE	Serine protease	↔	11/32	Wood *et al.* 1982
		↓	7/32	Nakano *et al.* 1986
		↔	10/15	Zubenko *et al.* 1986
		↓	52/20	Kumar *et al.* 1989
		↓	17/17	Sirvio *et al.* 1989
		↓	22/32	Kawakatsu *et al.* 1990
		↓	168/48	Reinikainen *et al.* 1990
AChE	Serine protease	↔	27/34	Hartikainen *et al.* 1992
		↔	22/78	Marksteiner *et al.* 2008

Table 2 *(continued)*. Candidate CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
ACE	Blood pressure regulation	↓	13/28	Zubenko *et al.* 1985
		↓	10/15	Zubenko *et al.* 1986
		↓	101/19	Miners *et al.* 2009
BACE1	Aspartic protease	↑	5/5	Holsinger *et al.* 2004
		↑	21/21	Holsinger *et al.* 2006
		↑	67/69	Zhong *et al.* 2007
		↑	60/37	Ewers *et al.* 2008
		↑	87/33	Zetterberg *et al.* 2008
		↑	17/12	Mulder *et al.* 2010
		↑	30/19	Ewers *et al.* 2011
		↔	25/16	Wu *et al.* 2011
		↔	75/65	Rosén *et al.* 2012
TACE	Metalloprotease	↑	32/27	Jiang *et al.* 2011
Cathepsin D	Aspartic protease	↓	43/43	Castaño *et al.* 2006
Hemopexin	Heme binding	↑	43/43	Castaño *et al.* 2006
Somatostatin	Neuropeptide	↓	11/32	Wood *et al.* 1982
		↓	35/26	Francis *et al.* 1984
		↓	10/21	Serby *et al.* 1984
		↓	10/9	Raskind *et al.* 1986
		↓	75/19	Reinikainen *et al.* 1987
		↓	12/15	Sunderland *et al.* 1987
		↓	25/8	Davis *et al.* 1988
		↓	168/48	Reinikainen *et al.* 1990
		↓	60/12	Molchan *et al.* 1991
		↓	27/34	Hartikainen *et al.* 1992
		↓	13/15	Martinez *et al.* 1993b
		↓	49/13	Molchan *et al.* 1993
		↓	36/40	Heilig *et al.* 1995
Cg	Neuroendocrine secretion	↔	29/9	Blennow *et al.* 1995a
		↓	10/10	Abdi *et al.* 2006
		↓	39/55	Hu *et al.* 2007
		↓	113/28	Simonsen *et al.* 2007
		↑	66/33	Hu *et al.* 2010
		↑	91/242	Craig-Schapiro *et al.*
		↓	24/24	Perrin *et al.* 2011
Secretogranin	Neuroendocrine secretion	↓	10/10	Abdi *et al.* 2006
		↓	39/55	Hu *et al.* 2007
		↓	24/24	Perrin *et al.* 2011
VSNL1	Calcium sensor protein	↑	98/211	Tarawneh *et al.* 2011
		↑	61/40	Luo *et al.* 2013
ApoAI	Lipid metabolism	↓	15/12	Davidsson *et al.* 2002
		↓	7/7	Puchades *et al.* 2003
		↓	43/43	Castaño *et al.* 2006
		↓	47/43	Roher *et al.* 2009
ApoAII	Lipid metabolism	↑	10/10	Abdi *et al.* 2006
ApoE	Cholesterol transport	↓	72/84	Lehtimäki *et al.* 1995
		↔	20/10	Merched *et al.* 1998

Table 2 *(continued)*. Candidate CSF biomarkers for Alzheimer's disease

Biomarker	Function	Findings	n (AD/control)	References
ApoE	Cholesterol transport	↔	83/88	Molina *et al.* 1999
		↑	76/34	Yamauchi *et al.* 1999
		↑	27/70	Rösler *et al.* 2001
		↔	32/10	Csernansky *et al.* 2002
		↓	15/12	Davidsson *et al.* 2002
		↓	7/7	Puchades *et al.* 2003
		↑	52/44	Finehout *et al.* 2007
		↑	12/12	Sihlbom *et al.* 2008
		↓	47/43	Roher *et al.* 2009
		↔	66/33	Hu *et al.* 2010
		↔	91/242	Craig-Schapiro *et al.*
		↔	24/24	Perrin *et al.* 2011
		↓	33/20	Vafadar *et al.* 2012
Apo H	Multifunction	↑	10/10	Abdi *et al.* 2006
RBP	Retinol carrier	↑	15/12	Davidsson *et al.* 2002
		↓	7/7	Puchades *et al.* 2003
		↑	10/10	Abdi *et al.* 2006
		↓	30/30	Jung *et al.* 2008
S100A	Calcium binding	↑	4/4	Qin *et al.* 2009
		↓	24/24	Perrin *et al.* 2011
S100B	Calcium binding	↔	68/25	Peskind *et al.* 2001
		↑	31/49	Petzold *et al.* 2003
		↑	18/14	Jesse *et al.* 2009
SORL1	Neuronal ApoE receptor	↓	13/13	Ma *et al.* 2009
		↑	29/27	Ikeuchi *et al.* 2010
NCAM	Cell adhesion	↑	3/3	Yin *et al.* 2009
		↑	137/30	Buchhave *et al.* 2010
		↓	66/33	Hu *et al.* 2010
		↓	24/24	Perrin *et al.* 2011
Substance P	Neuropeptide	↓	13/15	Martinez *et al.* 1993b
		↔	27/70	Rösler *et al.* 2001
		↓	38/19	Ernst *et al.* 2010
AD7c-NTP	Membrane phosphoprotein	↑	89/18	Monte *et al.* 1997
		↑	35/16	Kahle *et al.* 2000

↑ increased; ↓ decreased; ↔ no significant alterations. Control refers to healthy subjects.

NfH: Neurofilament heavy chain; *NfL*: Neurofilament light chain; *TG*: Transglutaminase; *sAPP*: Soluble amyloid precursor protein; *sAPPβ*: Soluble amyloid precursor protein β; *sAPPα*: Soluble amyloid precursor protein α; *GFAP :* Glial fibrillary acidic protein*; IL-1 beta*: Interleukin-1 beta; *sIL-1R*: Soluble interleukin 1 receptor; *IL-6*: Interleukin 6; *sIL-6R*: Soluble interleukin 6 receptor; *Gp130*: Glycoprotein 130; *IL-11*: Interleukin 11; *IL-7*: Interleukin 7; *TRAIL-R3*: TNF-related apoptosis-inducing ligand receptor; *MIF*: Macrophage migration inhibitory factor; *PG*: Prostaglandins; *C3*: Complement component 3; *C4*: Complement component 4; *MCP-1*: Monocyte chemotactic protein 1; *TNF-α*: Tumor necrosis factor alpha; *sTNFR:* Soluble TNF receptor; *GAP-43*: Growth associated protein 43;

TGFβ-1: Transforming growth factor beta 1; *PEDF*: Pigment epithelium-derived factor; *VEGF*: Vascular endothelial growth factor; *VGF:* Nerve growth factor inducible*; HNE*: 4-Hydroxynonenal; *8-OHdG*: 8-Hydroxydeoxyguanosine; *3-NT*: 3-Nitrotyrosine; *SOD1*: Superoxide dismutase 1; *hFABP*: Heart-type fatty acid binding protein; *MMP-2*: Matrix metalloproteinase 2; *MMP-3*: Matrix metalloproteinase 3; *MMP-9*: Matrix metalloproteinase 9; *MMP-10*: Matrix metalloproteinase 10; *PP*: Pancreatic polypeptide; *TIMP-1*: Tissue inhibitor of metalloproteinase 1; TIMP-2: Tissue inhibitor of metalloproteinase 2; *IGF-1*: Insulin-like growth factor 1; *IGFBP*: Insulin-like growth factor binding protein; *ACT*: α1-Antichymotrypsin; *ZAG*: Zinc α2-glycoprotein; *ATIII*: Antithrombin III; *CNDP1*: Carnosinase 1; HVA: Homovanillic acid; *5HIAA*: 5-hydroxy-indoleacetic acid; *MHPG*: 3-methoxy-4-hydroxyphenylglycol; *AChE*: Acetylcholinesterase; *ACE*: Angiotensin converting enzyme; *BACE1*: Beta-site amyloid precursor protein (APP)-cleaving enzyme 1; *TACE*: Tumor necrosis factor-α-converting enzyme; *Cg*: Chromogranin; *VSNL1*: Visinin-like protein 1; *Apo AI*: Apolipoprotein A1; *Apo AII*: Apolipoprotein A2; *Apo E*: Apolipoprotein E; *Apo H*: Apolipoprotein H (β2-glycoprotein I); *RBP*: Retinol-binding proteins; *S100A*: Calcium-binding protein A; *S100B*: Calcium-binding protein B; *SORL1*: Sortilin-related receptor*; NCAM*: Neural cell adhesion molecule; *AD7c-NTP*: AD-associated neuronal thread protein.

These complementary candidate biomarkers are more controversial and for most of them different studies reported different changes (increased and decreased levels). Neurofilament proteins have been suggested as strong candidates, particularly to differentiate AD from other related dementias (Sjogren et al., 2000b; de Jong et al., 2007; Petzold et al., 2007). These proteins are major neuronal structural elements and increased levels reflect axonal degeneration. The same principle applies to other cytoskeletal proteins as GFAP. Some other molecules pointed as more promising are closely related with AD pathology, like BACE-1, APP fragments or cholesterol carriers and metabolites (Cedazo-Minguez et al., 2010), despite the variability between studies seen so far. Inflammatory mediators are usually elevated whereas neurotrophic factors change in the opposite direction, as expected given the pathological mechanisms. VSNL1 (also called VILIP-1) is a calcium/binding protein and it is released into CSF from damaged neurons. In accordance, several studies reported elevated levels, raising the hope that it could be a useful biomarker for AD (Lee et al., 2008).

4. Parkinson's disease

Parkinson's disease (PD) is the second most common neurological disorder after Alzheimer's disease, affecting over 6.3 million people worldwide, a prevalence that is expected to double by 2030 (European Brain Council, 2011). In the USA alone, the combined direct and indirect costs of this disease are projected to be nearly US$25 million per year (Parkinson's Disease Foundation, 2013).

More than 90% of the cases are sporadic, where no cause is identified, while 5 to 10% represent familial inherited forms resulting from mutations in genes involved in the disease (Kroksveen *et al.*, 2011). The mean age of onset for idiopathic PD is approximately 60 years.

4.1. Clinical presentation and diagnosis

As for other neurodegenerative diseases, most of the symptoms in PD occur after a loss of more than 70% of dopaminergic neurons in *substantia nigra* within the brain stem. This area controls motor functions, which explains the main symptomatology, such as resting tremor, rigidity, bradikynesia and postural instability. Other less frequent motor symptoms are the freezing phenomenon and decreased facial movements or expressions (Fahn, 2003). Along with motor impairment often arise additional non-motor symptoms, including constipation, olfaction loss, sleep disturbances, mood disorders, depression, cognitive deficits, sexual and bladder problems, among others. These symptoms can even precede the motor ones, and could be helpful to the diagnostic, despite being shared with some related diseases (Waragai *et al.*, 2013).

Making an accurate diagnosis is difficult, particularly at early stages. It is commonly based on the presence of two of the three key signs: resting tremor, bradikynesia and rigidity. There are no standard diagnostic criteria, so diagnosis usually relies on this clinical information and neurological exams, which may include imaging techniques like MRI, CT and PET-Scan. Additional tests could be used for trying to exclude other diseases that could mimic PD, since the absolute diagnosis can only be made by brain autopsy. One of these tests is a positive response to levodopa, a drug that temporarily restores dopamine levels in the brain (Jankovic, 2008).

4.2. Pathological features

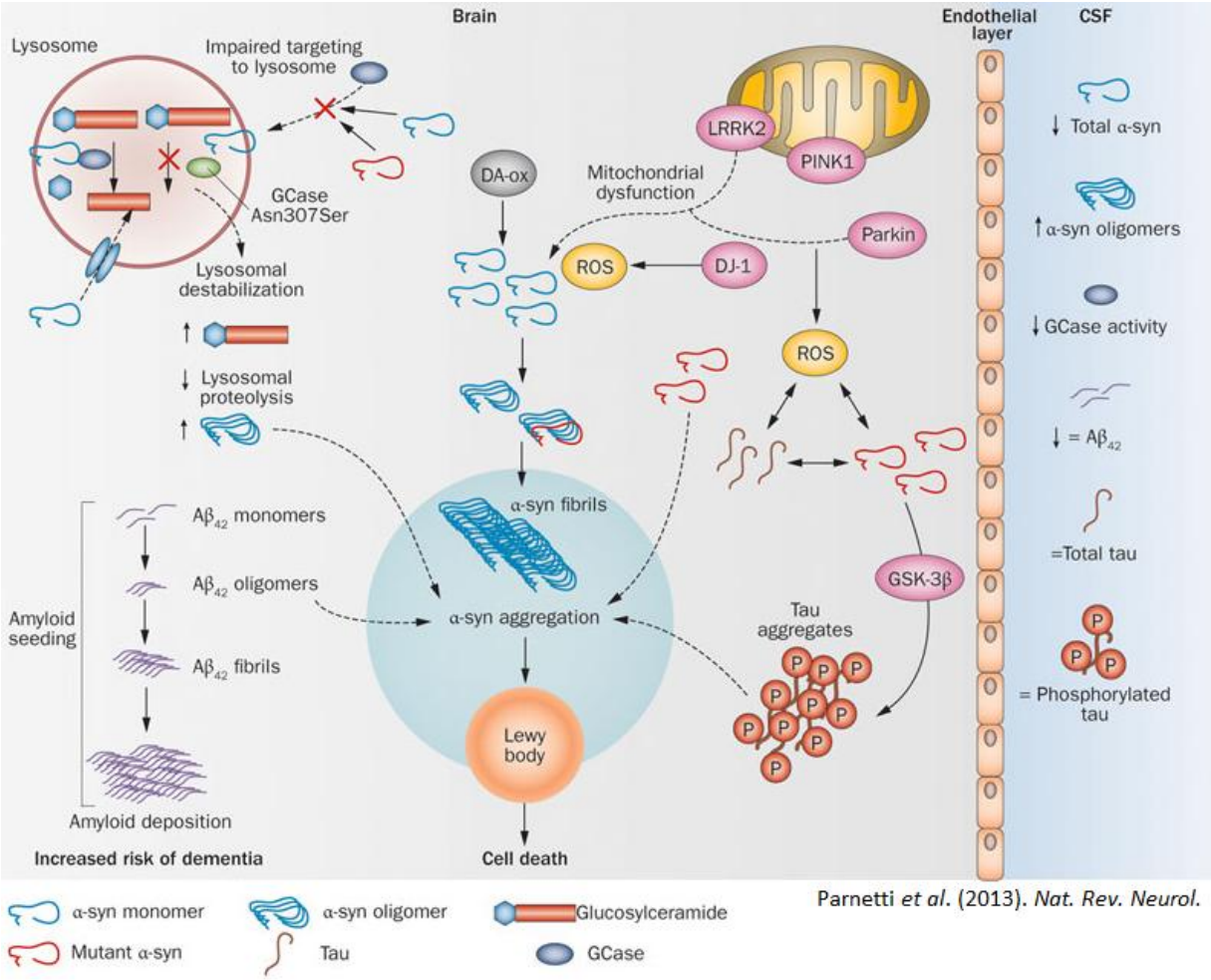
The most important neuropathological feature of Parkinson's disease is dopaminergic cell loss within the substantia nigra along with the deposition of intracellular protein-rich inclusions named Lewy bodies (LB) (Dickson *et al.*, 2009). These inclusions are composed mainly by fibrillar aggregates of α-synuclein protein. Dopaminergic neurons in the substantia nigra project to the striatum, therefore the nigral cell loss results in the depletion of striatal dopamine, ultimately responsible for characteristic motor symptoms. However, as the non-motor clinical signs could suggest, α-synuclein pathology extends to other brain regions and to nondopaminergic cell types (Rodriguez-Oroz *et al.*, 2009).

Regardless of being a complex disease and the possible involvement of different susceptibility genes and environmental factors, aggregation of α-synuclein is proposed as the central event leading to neurotoxicity. It is still not clear which forms are more toxic, oligomers or fibrils, and how exactly these abnormalities lead to neurodegeneration, or even the role of mitochondrial dynamics and response to oxidative stress (Shulman *et al.*, 2011). Most likely, toxic forms of α-synuclein may overwhelm molecular chaperones, lysosomes and the ubiquitin proteasome system, leading to mitochondrial dysfunction, disruption of axonal transport and synaptic loss (Lee *et al.*, 2006).

4.3. CSF biomarkers in PD

Similarly to AD and other neurodegenerative disorders, the most promising biomarkers for PD are based in suggested pathogenic pathways, either specific (e.g. α-synuclein and DJ-1) or related with more general neurodegenerative mechanisms like lysosomal and mitochondrial dysfunction, oxidative stress and neuroinflammation (Parnetti *et al.*, 2013)(Figure 3).

Figure 3 (next page). Schematic representation of pathogenic pathways underlying putative biomarkers for Parkinson's disease. The aggregation and deposition of α-synuclein is triggered by oxidative species and mitochondrial and lysosomal dysfunction, but could also exacerbate those same malfunctions. As a result, levels of α-synuclein decrease in CSF and markers of neuroinflammation and oxidative stress are usually elevated. Dementia in PD could also be linked to the same markers of AD, namely amyloid peptides and tau protein. (Molecules name abbreviations are detailed in Table 3).



Parnetti *et al.* (2013). *Nat. Rev. Neurol.*

In Table 3 are summarized the major findings for those putative biomarkers, with at least one study reporting an increase or decrease value.

Table 3. Candidate CSF biomarkers for Parkinson's disease

Biomarker	Function	Findings	n (PD/control)	References
Key markers				
α-Synuclein	Poorly understood (Potential microtubule associated protein; chaperone)	↔	12/10	Borghi *et al.* 2000
		↓	33/38	Tokuda *et al.* 2006
		↓	8/13	Mollenhauer *et al.* 2008
		↔	15/55	Ohrfelt *et al.* 2009
		↓	117/132	Hong *et al.* 2010
		↓	32/28	Tokuda *et al.* 2010
		↔	38/20	Foulds *et al.* 2011
		↓	324/99	Mollenhauer *et al.* 2011
		↔	23/29	Park *et al.* 2011
		↓	38/32	Parnetti *et al.* 2011
		↓	126/137	Shi *et al.* 2011
		↔	58/183	Aerts *et al.* 2012
		↓	11/11	Tateno *et al.* 2012
		↓	209/204	Wang *et al.* 2012

Table 3 *(continued)*. Candidate CSF biomarkers for Parkinson's disease

Biomarker	Function	Findings	n (PD/control)	References
α-Synuclein	Poorly understood	↓	78/48	Mollenhauer *et al.* 2013
		↓	53/50	van Dijk *et al.* 2013c
		↓	38/52	Wennström *et al.* 2013
DJ-1	Transcription regulator	↑	40/38	Waragai *et al.* 2006
		↓	117/132	Hong *et al.* 2010
		↓	126/137	Shi *et al.* 2011
Markers related with axonal degeneration				
$A\beta_{42}$	Poorly understood (activation of kinases; transcription factor)	↔	15/19	Kanemaru *et al.* 2000
		↔	23/32	Sjogren *et al.* 2000
		↓	15/17	Sjogren *et al.* 2002
		↔	48/32	Holmberg *et al.* 2003
		↔	12/24	Lins *et al.* 2004
		↔	30/34	Verbeek *et al.* 2004
		↓	96/41	Mollenhauer *et al.* 2006
		↔	11/19	Mollenhauer *et al.* 2007
		↓	20/20	Parnetti *et al.* 2008
		↓	40/95	Zhang *et al.* 2008
		↓	40/30	Compta *et al.* 2009
		↓	109/36	Alves *et al.* 2010
		↓	122/150	Montine *et al.* 2010
		↔	32/30	Přikrylová *et al.* 2010
		↔	38/32	Parnetti *et al.* 2011
		↓	126/137	Shi *et al.* 2011
Tau protein	Microtubule stabilization	↔	15/31	Blennow *et al.* 1995
		↔	73/77	Arai *et al.* 1997
		↔	26/25	Molina *et al.* 1997
		↔	115/15	Jansen *et al.* 1998
		↔	29/16	Kahle *et al.* 2000
		↔	15/19	Kanemaru *et al.* 2000
		↔	23/32	Sjogren *et al.* 2000
		↔	15/17	Sjogren *et al.* 2001
		↔	12/24	Lins *et al.* 2004
		↔	14/61	Paraskevas *et al.* 2005
		↑	96/41	Mollenhauer *et al.* 2006
		↑	11/19	Mollenhauer *et al.* 2007
		↔	10/27	Borroni *et al.* 2008
		↔	20/20	Parnetti *et al.* 2008
		↓	40/95	Zhang *et al.* 2008
		↔	40/30	Compta *et al.* 2009
		↔	109/36	Alves *et al.* 2010
		↔	122/150	Montine *et al.* 2010
		↑	32/30	Přikrylová *et al.* 2010
		↔	38/32	Parnetti *et al.* 2011
		↓	126/137	Shi *et al.* 2011
NfH	Axonal structure protein	↔	22/45	Brettschneider *et al.*
		↔	20/40	Steinacker *et al.* 2011
TG	Protein cross-linking	↑	54/34	Vermes *et al.* 2004

Table 3 *(continued)*. Candidate CSF biomarkers for Parkinson's disease

Biomarker	Function	Findings	n (PD/control)	References
sAPP	Neurotrophic factor	↓	10/9	Henriksson *et al.* 1991
Markers related with inflammation and immune response				
IL-1 beta	Immune response	↔	20/42	Pirtilla *et al.* 1994
		↑	22/12	Blum-Degen *et al.* 1995
IL-6	Immune response	↑	22/12	Blum-Degen *et al.* 1995
		↑	22/22	Müller *et al.* 1998
IL-8	Immune response	↑	40/95	Zhang *et al.* 2008
C3	Inflammatory response	↓	10/9	Finehout *et al.* 2005
		↓	23/24	Guo *et al.* 2009
C4	Inflammatory response	↓	10/9	Finehout *et al.* 2005
		↓	23/24	Guo *et al.* 2009
		↓	6/6	Wang *et al.* 2013
Factor B	Inflammatory	↓	10/9	Finehout *et al.* 2005
Dermcidin	Immune response	↓	23/24	Guo *et al.* 2009
MCP-1	Inflammatory response	↑	25/16	Nagata *et al.* 2007
		↔	8/13	Choi *et al.* 2008
TNF-α	Immune response	↑	15/16	Mogi *et al.* 1994
		↑	38/10	Le *et al.* 1999
Neopterin	Immune response	↓	18/28	Fujishiro *et al.* 1990
		↑	22/11	Widner *et al.* 2002
Markers related with neuroprotection				
BDNF	Neurotrophic factor	↓	40/95	Zhang *et al.* 2008
		↑	24/24	Salehi *et al.* 2009
GAP-43	Axonal growth	↓	23/32	Sjogren *et al.* 2000
TGFβ-1	Growth factor	↑	30/16	Vawter *et al.* 1996
		↔	24/25	Rota *et al.* 2006
PEDF	Neurotrophic factor	↑	23/24	Guo *et al.* 2009
Neurosin	Serine protease	↓	38/52	Wennström *et al.* 2013
Clusterin	Chaperone	↔	18/11	Lidström *et al.* 2001
		↓	23/24	Guo *et al.* 2009
		↑	3/3	Yin *et al.* 2009
		↑	32/30	Přikrylová *et al.* 2010
		↑	43/49	Maarouf *et al.* 2012
		↔	52/50	van Dijk *et al.* 2013a
Cystatin C	Cysteine protease inhibitor	↓	51/52	Maetzler *et al.* 2010
		↔	32/30	Přikrylová *et al.* 2010
		↔	18/15	Yamamoto *et al.* 2010
β2microglobulin	HLA complex	↓	59/44	Mogi *et al.* 1989
		↑	40/95	Zhang *et al.* 2008
		↔	56/24	Constantinescu *et al.* 2010b
Markers related with oxidative stress				
HNE	Lipid peroxidation	↑	10/10	Selley. 1998
8-OHdG	DNA oxidative damage	↑	48/21	Kikuchi *et al.* 2002
		↑	48/13	Gmitterová *et al.* 2009
		↑	20/20	Isobe *et al.* 2010
SOD1	Detoxification	↔	26/26	Marttila *et al.* 1988
		↔	12/58	De Deyn *et al.* 1998

Table 3 *(continued)*. Candidate CSF biomarkers for Parkinson's disease

Biomarker	Function	Findings	n (PD/control)	References
SOD1	Detoxification	↓	22/41	Boll *et al.* 2008
		↑	23/24	Guo *et al.* 2009
		↔	6/6	Wang *et al.* 2013
Nitrate	NO biotransformation	↓	103/20	Kuiper *et al.* 1994b
		↔	11/17	Ikeda *et al.* 1995
		↔	31/38	Molina *et al.* 1996
		↔	20/21	Shukla *et al.* 2006
		↑	22/41	Boll *et al.* 2008
Haptoglobin	Hemoglobin binding	↑	10/10	Abdi *et al.* 2006
		↓	23/24	Guo *et al.* 2009
MDA	Lipid oxidation	↑	31/31	Ilic *et al.* 1998
		↑	34/34	Ilic *et al.* 1999
		↔	20/21	Shukla *et al.* 2006
Transferrin	Iron binding	↔	12/11	Loeffler *et al.* 1994
		↔	90/21	van Kamp *et al.* 1995
		↑	14/14	Sinha *et al.* 2009
Ceruloplasmin	Copper transport	↔	12/11	Loeffler *et al.* 1994
		↓	35/26	Boll *et al.* 1999
		↓	10/10	Abdi *et al.* 2006
		↓	22/41	Boll *et al.* 2008
Others				
TIMP-1	MMP-1 inhibitor	↑	13/41	Lorenzl et al. 2003
Glutamate	Excitotoxicity	↓	20/11	Ondarza *et al.* 1994
		↔	31/45	Jiménez-Jiménez *et al.*
		↓	10/10	Mally *et al.* 1997
		↔	108/21	Kuiper *et al.* 2000
DBH	Cathecolamine biosynthesis	↓	5/5	Matsui *et al.* 1981
		↓	-	Hurst *et al.* 1985
		↓	34/25	Mogi *et al.* 1988
		↔	35/34	Hartikainen *et al.* 1992
Transthyretin	Thyroid hormone binding	↓	23/24	Guo *et al.* 2009
		↓	3/3	Yin *et al.* 2009
		↑	43/49	Maarouf *et al.* 2012
		↑	103/72	Maetzler *et al.* 2012
IGF-1	Cell proliferation	↑	38/38	Mashayekhi *et al.* 2010
IGFBP	IGF binding protein	↑	38/38	Mashayekhi et al. 2010
α1-Antitrypsin	Protease inhibitor	↑	23/24	Guo *et al.* 2009
Autotaxin	Lipid signaling	↑	23/24	Guo *et al.* 2009
Tetranectin	Plasminogen binding	↓	11/10	Wang *et al.* 2010
		↓	6/6	Wang *et al.* 2013
Fibrinogen	Coagulation cascade	↔	10/10	Abdi *et al.* 2006
		↓	3/3	Yin *et al.* 2009
		↓	43/49	Maarouf *et al.* 2012
Osteopontin	Stress; inflammation	↑	30/30	Maetzler *et al.* 2007
Copper	Micronutrient	↑	24/34	Pall *et al.* 1987
		↔	11/11	Gazzaniga *et al.* 1992
		↔	37/37	Jiménez-Jiménez *et al.*

Table 3 *(continued)*. Candidate CSF biomarkers for Parkinson's disease

Biomarker	Function	Findings	n (PD/control)	References
Copper	Micronutrient	↑	35/26	Boll *et al.* 1999
		↑	22/41	Boll *et al.* 2008
		↑	20/15	Hozumi *et al.* 2011
Orexin	Neurotransmitter	↔	7/48	Ripley *et al.* 2001
		↓	19/19	Drouot *et al.* 2003
		↔	10/20	Baumann *et al.* 2005
		↓	9/17	Fronczek *et al.* 2007
HVA	Dopamine metabolite	↓	31/10	Van Woert *et al.* 1970
		↓	23/25	Chase *et al.* 1972
		↓	11/24	Curzon *et al.* 1972
		↓	26/11	Gumpert *et al.* 1973
		↓	75/15	Davidson *et al.* 1977
		↓	11/30	Ichikawa. 1986
		↓	36/19	Jolkkonen *et al.* 1986
		↔	10/15	Zubenko *et al.* 1986
		↓	14/4	Kurlan *et al.* 1988b
		↓	35/34	Hartikainen *et al.* 1992
		↓	38/12	Strittmatter *et al.* 1992
		↓	61/26	Chia *et al.* 1993
		↓	23/15	García *et al.* 1995
		↓	20/16	Cheng *et al.* 1996
		↔	35/11	Strittmatter *et al.* 1996
		↓	11/13	Kanemaru *et al.* 1998
5HIAA	Serotonin metabolite	↓	27/10	Van Woert *et al.* 1970
		↓	23/25	Chase *et al.* 1972
		↓	11/24	Curzon *et al.* 1972
		↓	26/11	Gumpert *et al.* 1973
		↔	75/15	Davidson *et al.* 1977
		↓	11/30	Ichikawa. 1986
		↓	35/34	Hartikainen *et al.* 1992
		↔	38/12	Strittmatter *et al.* 1992
		↔	61/26	Chia *et al.* 1993
		↑	23/15	García *et al.* 1995
		↔	35/11	Strittmatter *et al.* 1996
AChE	Serine protease	↔	36/19	Jolkkonen *et al.* 1986
		↔	10/15	Zubenko *et al.* 1986
		↔	11/5	Ruberg *et al.* 1986
		↔	13/19	Ruberg *et al.* 1987
		↔	16/9	Manyam *et al.* 1990b
		↓	35/34	Hartikainen *et al.* 1992
		↔	103/20	Konings *et al.* 1995
ACE	Blood pressure regulation	↓	10/30	Zubenko *et al.* 1985
		↓	10/15	Zubenko *et al.* 1986
		↑	106/20	Konings *et al.* 1994
β-glucosidase	Glycolipid metabolism	↓	12/20	Balducci *et al.* 2007
		↔	58/52	van Dijk *et al.* 2013b
Somatostatin	Neuropeptide	↓	39/-	Dupont *et al.* 1982

Table 3 *(continued)*. Candidate CSF biomarkers for Parkinson's disease

Biomarker	Function	Findings	n (PD/control)	References
Somatostatin	Neuropeptide	↓	36/19	Jolkkonen *et al.* 1986
		↔	-	Volicer *et al.* 1986
		↓	-	Unger *et al.* 1988
		↓	68/6	Jost *et al.* 1990
		↓	35/11	Masson *et al.* 1990
		↔	35/34	Hartikainen *et al.* 1992
		↓	38/12	Strittmatter *et al.* 1992
		↑	33/26	Espino *et al.* 1995
		↓	35/11	Strittmatter *et al.* 1996
CgA	Neuroendocrine	↓	10/10	Kaiserová *et al.* 2013
VDBP	Vitamin D transport	↔	10/10	Abdi *et al.* 2006
		↑	40/95	Zhang *et al.* 2008
ApoAI	Lipid metabolism	↓	20/91	Harrington *et al.* 1984
		↓	40/95	Zhang *et al.* 2008
		↓	3/3	Yin *et al.* 2009
		↑	11/10	Wang *et al.* 2010
		↓	43/49	Maarouf *et al.* 2012
		↑	6/6	Wang *et al.* 2013
ApoAII	Lipid metabolism	↓	40/95	Zhang *et al.* 2008
ApoE	Cholesterol transport	↔	10/10	Abdi *et al.* 2006
		↓	40/95	Zhang *et al.* 2008
		↑	23/24	Guo *et al.* 2009
		↑	43/49	Maarouf *et al.* 2012
		↑	23/24	Guo *et al.* 2009
Apo H	Multifunction	↓	10/10	Abdi *et al.* 2006
ADH	Peptide hormone	↓	11/21	Sundquist *et al.* 1983
		↓	-	Olsson *et al.* 1987
NPY	Neuropeptide	↔	8/9	Yaksh *et al.* 1990
		↓	10/20	Martignoni *et al.* 1992
Substance P	Neuropeptide	↓	-	Pezzoli *et al.* 1994
		↔	8/14	Matsuishi *et al.* 1996a
		↔	23/16	Matsuishi *et al.* 1999
Enkephalins	Nociception regulation	↓	8/9	Yaksh *et al.* 1990
		↓	32/13	Baronti *et al.* 1991
		↑	-	Pezzoli *et al.* 1994
CCK	Fat, protein digestion	↓	20/68	Lotstra *et al.* 1985

↑ increased; ↓ decreased; ↔ no significant alterations; Control refers to healthy subjects.

DJ-1: Parkinson disease (autosomal recessive, early onset) 7 (PARK7); *Aβ42*: Beta amyloid; *NfH*: Neurofilament heavy chain; *NfL*: Neurofilament light chain; *TG*: Transglutaminase; *sAPP*: Soluble amyloid precursor protein;*IL-1 beta*: Interleukin-1 beta; ; *IL-2*: Interleukin 2; *IL-6*: Interleukin 6; *IL-8*: interleukin 8; *C3*: Complement component 3; *C4*: Complement component 4; *MCP-1*: Monocyte chemotactic protein 1; *TNF-α*: Tumor necrosis factor alpha; *BDNF*: Brain derived neurotrophic factor; *GAP-43*: Growth associated protein 43; *TGFβ-1*: Transforming growth factor beta 1; *PEDF*: Pigment epithelium-derived factor; *Flt3*: FMS-like tyrosine kinase 3; *HNE*: 4-Hydroxynonenal; *8-OHdG*: 8-

Hydroxydeoxyguanosine; *SOD1*: Superoxide dismutase 1; *SOD2*: Superoxide dismutase 2; *GPX*: Glutathione peroxidase; *MDA*: Malondialdehyde; *MMP-2*: Matrix metalloproteinase 2; *MMP-9*: Matrix metalloproteinase 9; *TIMP-1*: Tissue inhibitor of metalloproteinase 1; TIMP-2: Tissue inhibitor of metalloproteinase 2; *DBH:* Dopamine beta hydroxylase; *IGF-1*: Insulin-like growth factor 1; *IGFBP*: Insulin-like growth factor binding protein; *HVA*: Homovanillic acid; *5HIAA*: 5-hydroxy-indoleacetic acid; *MHPG*: 3-methoxy-4-hydroxyphenylglycol; *AChE*: Acetylcholinesterase; *ACE*: Angiotensin converting enzyme; *CgA*: Chromogranin A; *VDBP*: vitamin D binding protein; *Apo AI*: Apolipoprotein A1; *Apo AII*: Apolipoprotein A2; *Apo E*: Apolipoprotein E; *Apo H*: Apolipoprotein H (β2-glycoprotein I); *AST*: Aspartate aminotransferase; *ADH*: Antidiuretic hormone; *NPY*: Neuropeptide Y; *CCK*: Cholecystokinin 8.

In contrast with Alzheimer's disease, there is still no validated biomarker for PD, but some promising candidates are emerging. This is particularly true for those species more related with pathogenesis, such as α-syn, DJ-1, $A\beta_{42}$ and tau protein (Nyhlén *et al*., 2010). Aggregation and plaque deposition of α-syn and Aβ42 is responsible for the low levels found in CSF. Although DJ-1 have been associated with PD in familial and sporadic forms, probably acting as a protease or chaperone, the results of different studies are still inconclusive and data is inconsistent (Constantinescu *et al*., 2013). On the other hand, biomarkers reflecting lysosomal dysfunction, pointed as an early event in PD pathogenesis, could be useful for complementing others in order to achieve a correct diagnosis (Parnetti *et al*., 2013). As expected, markers of oxidative stress and inflammation are generally elevated in PD patients. Two related candidate biomarkers, ceruloplasmin and copper, present low and high levels respectively, in almost all CSF studies. Cooper acts as an antioxidant when bound to proteins such as ceruloplasmin but when in its free form the effect is just the opposite. The low levels of cooper binding proteins in PD are probably responsible for the release and high levels of free metal (Boll *et al*., 2008).

The limitations presented by the lack of sufficient biomarker studies are being addressed by some global initiatives, such as the Parkinson Progression Marker Initiative, raising the hope of reaching validated useful biomarkers in a near future (Parkinson Progression Marker Initiative, 2011).

5. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also called Lou Gehrig's disease, is the most common neuromuscular disease, characterized by progressive degeneration and death of motor neurons, leading to death within 3 to 5 years after disease onset. It generally affects more men than women, at ages among 40 and 70 years (ALS Foundation for Life, 2013). The global annual incidence is estimated to be 0.4 to 3.7 per 100,000 individuals and the prevalence ranged from 0.2 to 1.2 per 10,000. The costs for caring just one patient with ALS could reach US$200,000 a year (Chio *et al.*, 2012).

About 90 to 95% of cases are labeled sporadic, since the patients do not seem to have any clear associated risk factors or a family history for ALS. The remaining cases are inherited, and mutations in more than ten different genes have been found to cause familial ALS. More than 50% of all familial cases (and also some sporadic) results from defects in C9orf72 and SOD1 genes (Kruger *et al.*, 2013).

5.1. Clinical presentation and diagnosis

The disease usually becomes apparent with symptoms like fasciculations, muscular cramps and weakness mainly focal and unilateral, coordination and speech impairments and swallowing difficulties. According to the part of the body first affected, the disease could be classified as classic, bulbar, limb, pyramidal and respiratory, to give some examples (Chio *et al.*, 2011). As the disease progress, symptoms spread to other body parts and eventually the individuals will not be able to stand or walk, and will experience serious difficulties in eating and breeding. In most cases the weakness of respiratory muscles is responsible for respiratory failure and consequent patient's death. Since cognitive functions are mostly intact, many patients could also suffer from anxiety and depression (National Institute of Neurologic Disorders and Stroke, 2013).

Similarly to almost all neurodegenerative diseases, the clinical diagnosis of ALS is difficult, particularly at early stages, but the presence of upper and lower motor neuron signs is strongly suggestive. It is based on El Escorial and the Awaji criteria, and a full medical history and neurologic evaluation could help to differentiate ALS from other disorders. At the same time, some other exams like MRI and electromyography (EMG) could detect ALS related alterations, but most importantly can reveal other causes for the symptoms (Brooks *et al.*, 2000; de Carvalho *et al.*, 2008).

5.2. Pathological features

The motor neurons affected and surrounding reactive astrocytes show different inclusion bodies as pathological hallmarks (Barbeito *et al.*, 2004). The most common are ubiquitinated inclusions, which suggest that the proteasome pathway is activated in this disease, and they are classified as Lewy body-like hyaline inclusions and skein-like inclusions (Kawashima *et al.*, 1998). Some other proteins identified in these aggresomes include SOD1, TDP-43, FUS and neurofilament proteins. Additionally, is possible to find Bunina bodies, which are cystatin C containing inclusions (Lowe, 1994; Sasaki *et al.*, 1994).

Numerous mechanisms have been proposed for the pathological process in ALS, but most researchers agree that is possibly a combination of some or all that leads to the development of disease (Pasinelli *et al.*, 2006). Mutated or misfolded proteins from inclusion bodies could be linked to defective axonal transport, Golgi fragmentation and ER stress. The excitotoxicity also appears to have an important role and could occur by exposure to excitotoxins, overactivation of glutamate receptors, oxidative stress, dysfunctions in calcium homeostasis or even cytoskeletal abnormalities with accumulation of neurofilaments. The resulting mitochondrial dysfunction and neuroinflammation can induce apoptosis and neuronal death (Strong, 2001; Shaw, 2005; Murata *et al.*, 2008).

5.3. Putative CSF biomarkers for ALS

Similarly to the diseases described above, insights in the pathological mechanisms of ALS can be useful as a starting point for biomarker discovery. Some mechanisms and molecules involved in motor neuron degeneration that could be useful in biomarker development are represented in Figure 4 (Kiernan *et al.*, 2011). Table 4 summarizes the most relevant studies in this area for the more prominent candidates, with at least one report of increased or decreased levels in CSF.

Figure 4 (next page)**.** Schematic illustration of the main pathophysiological mechanisms proposed for ALS. Neurodegeneration could result from protein aggregation and consequent mitochondrial dysfunction, defects in calcium homeostasis and axonal transport, malfunction of neuroprotective enzymes like SOD1, and increased neuronal vulnerability to free radicals, glutamate excitotoxicity and inflammatory mediators.

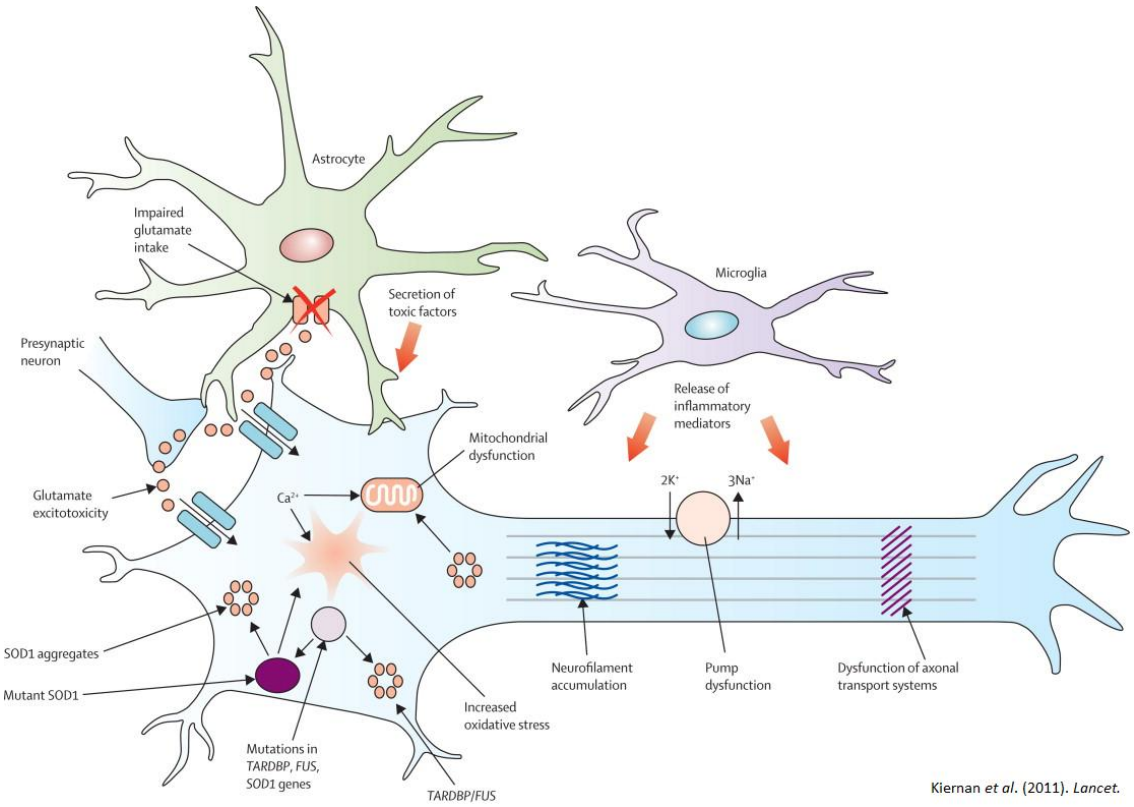


Table 4. Candidate CSF biomarkers for Amyotrophic lateral sclerosis

Biomarker	Function	Findings	n (ALS/control)	References
Markers related with neuroprotection				
TDP-43	DNA/RNA binding protein	↑	27/25	Steinacker *et al.* 2008
		↑	30/29	Kasai *et al.* 2009
		↑	27/50	Noto *et al.* 2011
PEDF	Neurotrophic factor	↑	-	Bilak *et al.* 1999
		↑	15/22	Kuncl *et al.* 2002
VEGF	Angiogenesis	↓	24/34	Devos *et al.* 2004
		↑	30/30	Ilzecka. 2004
		↓	20/20	Moreau *et al.* 2006
		↓	20/20	Just *et al.* 2007
		↓	42/16	Nagata *et al.* 2007
		↓	40/40	Moreau *et al.* 2009
		↑	42/34	Tateishi *et al.* 2010
		↑	50/50	Gupta *et al.* 2011
PGRN	Neurotrophic factor	↑	91/56	Philips *et al.* 2010
		↓	68/60	Steinacker *et al.* 2011
Cystatin C	Cysteine protease inhibitor	↓	23/31	Ranganathan *et al.* 2005
		↓	36/21	Pasinetti *et al.* 2006
		↓	14/29	Tsuji-Akimoto *et al.* 2009
		↓	100/141	Ryberg *et al.* 2010
		↓	44/69	Wilson *et al.* 2010
		↔	31/99	Yamamoto *et al.* 2010
		↓	23/46	Wilson *et al.* 2013

Table 4 *(continued)*. Candidate CSF biomarkers for Amyotrophic lateral sclerosis

Biomarker	Function	Findings	n (ALS/control)	References
TGFβ-1	Growth factor	↑	24/15	Ilzecka *et al*. 2002
S100b	Neurotrophic factor	↓	20/20	Süssmuth *et al*. 2003
		↓	75/28	Süssmuth *et al*. 2010
GDNF	Neurotrophic factor	↑	15/11	Grundström *et al*. 2000
FGF-2	Growth factor	↑	15/10	Johansson *et al*. 2003
Flt3	Neurotrophic factor	↑	23/23	Ilzecka. 2006
HGF	Growth factor	↑	12/11	Kern *et al*. 2001
		↑	10/32	Tsuboi *et al*. 2002
Markers related with axonal degeneration				
NfH	Axonal structure protein	↑	69/106	Brettschneider *et al*. 2006a
		↑	29/15	Reijn *et al*. 2009
		↑	50/73	Kuhle *et al*. 2010
		↑	71/92	Ganesalingam *et al*. 2011
		↑	10/6	Mendonça *et al*. 2011
		↑	68/60	Steinacker *et al*. 2011
		↑	150/140	Ganesalingam *et al*. 2013
NfL	Axonal structure protein	↑	12/45	Rosengren *et al*. 1996
		↑	11/5	Norgren *et al*. 2003
		↑	79/246	Zetterberg *et al*. 2007
		↑	29/15	Reijn *et al*. 2009
		↑	37/46	Tortelli *et al*. 2012
Tau protein	Microtubule stabilization	↔	11/17	Sjogren *et al*. 2002
		↑	20/20	Süssmuth *et al*. 2003
		↔	18/75	Jiménez-Jiménez *et al*. 2005
		↔	30/49	Brettschneider *et al*. 2006b
		↑	69/33	Brettschneider *et al*. 2006a
		↑	75/47	Süssmuth *et al*. 2010
TGases	Protein cross-linking	↑	17/21	Fujita *et al*. 1998
$A\beta_{42}$	Poor understood	↓	11/17	Sjogren *et al*. 2002
sAPP	Neurotrophic factor	↓	68/60	Steinacker *et al*. 2011
Markers related with inflammation and immune response				
IL-6	Immune response	↑	27/21	Sekizawa *et al*. 1998
		↔	20/20	Moreau *et al*. 2005
		↔	16/16	Klimek *et al*. 1995
IL-8	Immune response	↑	41/33	Mitchell *et al*. 2009
		↑	20/20	Kuhle *et al*. 2009
C3	Inflammatory response	↑	13/23	Annunziata *et al*. 1985
		↑	71/92	Ganesalingam *et al*. 2011
C4	Inflammatory response	↔	13/23	Annunziata *et al*. 1985
		↑	15/12	Tsuboi *et al*. 1994
G-CSF	Immune response	↑	37/33	Tanaka *et al*. 2006
		↑	42/34	Tateishi *et al*. 2010
MCP-1	Inflammatory response	↑	29/11	Wilms *et al*. 2003
		↑	16/29	Henkel *et al*. 2004
		↔	31/38	Simpson *et al*. 2004
		↑	27/30	Baron *et al*. 2005
		↑	37/33	Tanaka *et al*. 2006

Table 4 *(continued)*. Candidate CSF biomarkers for Amyotrophic lateral sclerosis

Biomarker	Function	Findings	n (ALS/control)	References
MCP-1	Inflammatory response	↑	42/16	Nagata *et al.* 2007
		↑	20/20	Kuhle *et al.* 2009
		↑	42/34	Tateishi *et al.* 2010
		↑	50/50	Gupta *et al.* 2011
		↑	44/29	Gupta *et al.* 2012
PGE2	Inflammatory response	↑	17/21	Almer *et al.* 2002
		↑	20/20	Iłzecka. 2003
TNF-α	Immune response	↑	42/34	Tateishi *et al.* 2010
Neopterin	Immune response	↑	12/39	Yoshida *et al.* 1999
Caspase-1	Inflammatory	↓	25/15	Iłzecka *et al.* 2001
Galactin-3	Immune response	↑	30/21	Zhou *et al.* 2010
RANTES	Immune response	↑	20/27	Rentzos *et al.* 2007
Markers related with oxidative stress				
HNE	Lipid peroxidation	↑	186/236	Beckman *et al.* 1993
		↑	69/49	Simpson *et al.* 2004
8-OHdG	DNA oxidative damage	↑	23/19	Bogdanov *et al.* 2000
		↑	7/14	Ihara *et al.* 2005
3-NT	Protein nitration	↑	18/14	Tohgi *et al.* 1999b
		↑	19/19	Tohgi et al. 1999c
		↔	14/19	Ryberg *et al.* 2004
		↔	10/6	Mendonça *et al.* 2011
SOD1	Detoxification	↔	66/37	Jacobsson *et al.* 2001
		↓	18/19	Boll *et al.* 2003
		↓	7/14	Ihara *et al.* 2005
		↑	30/22	Kokić *et al.* 2005
		↓	27/41	Boll et al. 2008
		↔	11/19	Frutiger *et al.* 2008
		↔	96/38	Zetterström *et al.* 2011
Glutathione	Detoxification	↑	12/15	Tohgi *et al.* 1999b
GPX	Peroxides	↑	40/30	Kuźma et al. 2006
Nitrate	NO transformation	↑	18/14	Tohgi *et al.* 1999b
		↑	18/19	Boll *et al.* 2003
		↔	14/25	Pirttilä *et al.* 2004
		↑	27/41	Boll et al. 2008
Iron	Radical generator	↔	30/22	Kokić *et al.* 2005
Uric acid	Excitotoxicity	↑	30/22	Kokić *et al.* 2005
Others				
MMP-2	Protein degradation	↔	18/41	Lorenzl *et al.* 2003
		↔	54/36	Fang *et al.* 2009
		↑	30/15	Niebroj-Dobosz *et al.* 2010
MMP-9	Protein degradation	↔	14/20	Beuche *et al.* 2000
		↑	54/36	Fang *et al.* 2009
		↓	30/15	Niebroj-Dobosz *et al.* 2010
TIMP-1	MMP-1 inhibitor	↔	14/20	Beuche *et al.* 2000
		↑	18/41	Lorenzl *et al.* 2003
		↔	30/15	Niebroj-Dobosz *et al.* 2010
Glutamate	Excitotoxicity	↑	377/106	Spreux-Varoquaux *et al.*

Table 4 *(continued)*. Candidate CSF biomarkers for Amyotrophic lateral sclerosis

Biomarker	Function	Findings	n (ALS/control)	References
Glutamate	Excitotoxicity	↓	78/78	Wuolikainen *et al.* 2011
EPO	Erythropoiesis	↓	30/49	Brettschneider *et al.* 2006b
		↑	20/20	Just *et al.* 2007
		↓	60/53	Brettschneider *et al.* 2007
		↓	15/20	Widl *et al.* 2007
		↓	30/15	Janik *et al.* 2010
Transthyretin	Thyroid hormone binding	↓	23/31	Ranganathan *et al.* 2005
		↓	100/141	Ryberg *et al.* 2010
VGF	Synaptogenesis	↓	36/21	Pasinetti *et al.* 2006
		↓	17/21	Zhao *et al.* 2008
Insulin	Metabolism	↓	24/40	Bilic *et al.* 2006
IGF-1	Cell proliferation	↔	14/25	Pirttilä *et al.* 2004
		↓	24/40	Bilic *et al.* 2006
		↑	54/50	Corbo *et al.* 2010
GH	Cell growth	↓	24/40	Bilic *et al.* 2006
DJ-1	Transcription	↑	30/9	Yamashita *et al.* 2010
GS	Glutamine synthesis	↑	8/35	Tumani *et al.* 1999
Substance P	Neuropeptide	↑	11/16	Matsuishi *et al.* 1999
Cytochrome	Electron transfer	↓	40/40	Iłzecka. 2007
7B2	Neuroendocrine	↑	23/31	Ranganathan *et al.* 2005

↑ increased; ↓ decreased; ↔ no significant alterations; Control refers to healthy subjects.

TDP-43: TAR DNA-binding protein 43; *PEDF*: Pigment epithelium-derived factor; *VEGF*: Vascular endothelial growth factor; *PGRN*: Progranulin; *TGFβ-1*: Transforming growth factor beta 1; *S100b*: S100 calcium binding protein B; *GDNF*: Glial cell-derived neurotrophic factor; *FGF-2*: Basic fibroblast growth factor; *Flt3*: FMS-like tyrosine kinase 3; *HGF*: Hepatocyte growth factor; *NfH*: Neurofilament heavy chain; *NfL*: Neurofilament light chain; *Aβ42*: Beta amyloid; *sAPP*: Soluble amyloid precursor protein; *IL-6*: Interleukin 6; *IL-8*: interleukin 8; *C3*: Complement component 3; *C4*: Complement component 4; *G-CSF*: Granulocyte colony-stimulating factor; *MCP-1*: Monocyte chemotactic protein 1; *PGE2*: Prostaglandin E2; *TNF-α*: Tumor necrosis factor alpha; *RANTES*: Regulated on activation, normal T cell expressed and secreted, also Chemokine (C-C motif) ligand 5; *HNE*: 4-Hydroxynonenal; *8-OHdG*: 8-Hydroxydeoxyguanosine; *3-NT*: 3-Nitrotyrosine; *SOD1*: Superoxide dismutase 1; *GPX*: Glutathione peroxidase; *MMP-2*: Matrix metalloproteinase 2; *MMP-9*: Matrix metalloproteinase 9; *TIMP-1*: Tissue inhibitor of metalloproteinase 1; TIMP-2: Tissue inhibitor of metalloproteinase 2; *EPO*: Erythropoietin; *VGF*: Nerve growth factor inducible; *IGF-1*: Insulin-like growth factor 1; *IGFBP-2*: Insulin-like growth factor binding protein 2; IGFBP-3: Insulin-like growth factor binding protein 3; *GH*: Growth hormone; *DJ-1*: Parkinson disease (autosomal recessive, early onset) 7 (PARK7); *GS*: Glutamine synthetase; *7B2*: Neuroendocrine protein 7B2.

The only drug approved for ALS (riluzole) only extends life span in 2 to 3 months, and most patients die within 3 years after disease onset (Kruger *et al.*, 2013). Therefore, the need for biomarkers, not only for early diagnosis but also for therapies development is even more important for this neurodegenerative disease. None of the above candidates have reached clinical significance and the future strategy could be a multiprotein profiling, making use of advances in molecular techniques. Nevertheless, the most promising candidates so far are probably TDP-43, neurofilament proteins and Cystatin C measurements (Noto *et al.*, 2011). TDP-43 is a DNA and RNA binding protein, playing a key role in ALS pathogenesis, as mutations in the gene encoding this protein are involved in sporadic and familial forms of the disease. The CSF levels are raised at early stages of the disease, though they gradually drop, probably resulting from the accumulation in neurons with disease progression (Kasai *et al.*, 2009). Neurofilament proteins are an important component of the axonal skeleton, playing a crucial role in maintaining integrity and axonal transport and their dysfunction have been implicated in motor neuron degeneration. Concentrations are raised in CSF due to neuronal loss, with a reported sensitivity and specificity higher than 90% compared to controls (Brettschneider *et al.*, 2006a). Cystatin C is a cysteine protease inhibitor having both a neurotoxic and a neuroprotective role and seems to be consistently decreased in ALS patients. It is also found in Bunina bodies, which could explain its low levels in CSF (Ranganathan et al., 2005). Some other findings have been significant for a better understanding of ALS pathogenesis and could be applied as biomarkers in the future. One example is high concentrations of excitatory amino acids (e.g. glutamate) in CSF, supporting the excitotoxicity hypothesis as a pathological mechanism (Turner *et al.*, 2009).

6. Polyglutamine diseases

Polyglutamine diseases are a group of neurodegenerative conditions with a genetic cause, resulting from a CAG triplet repeat expansion in a specific gene that produces a pathogenic protein containing an expanded tract of glutamines. These mutations could affect ten different genes, each one originating a specific disease. Some examples are Huntington's disease (HD) and several spinocerebellar ataxias (SCA), the most common being SCA3, also called Machado-Joseph disease (MJD) (Shao *et al.*, 2007).

Huntington's is the most common among all polyglutamine diseases with approximately 30,000 people diagnosed in USA and Canada and roughly 150,000 at risk. In Europe, the estimated prevalence is about 4 to 9 per 100,000 individuals, the lower limit being approximately the prevalence of all other polyglutamine diseases, particularly spinocerebellar ataxias. The impact is, however, disproportionate to that prevalence, since they tend to manifest in middle age and are progressive, resulting not only in enormous costs of care but also in lost earnings from individuals affected and possibly some family members (Paulson *et al.*, 2011).

6.1. Huntington's disease clinical features

Huntington's disease results from a mutation in the huntingtin (*HTT*) gene, with a CAG pathogenic repeat length of 36 to 121. The mutated protein inclusions are often found in nucleus and cytoplasm of neurons located in the striatum and cerebral cortex (Nakamura *et al.*, 2007).

The characteristic features include a progressive movement disorder (chorea), cognitive decline culminating in dementia and various psychiatric and behavioral symptoms. The course of the disease is slow and some early symptoms include mood swings, depression, troubles in learning or making decisions and memory impairments. Later it could lead to absence of speech, swallowing and feeding difficulties, walking problems and finally to total loss of independence (Ross *et al.*, 2011). Usually patients die before the age of 60, the disease extending for an average of 20 years. The diagnosis can be made by a genetic test, generally coupled with a complete medical history and neurological and laboratory tests (Davis *et al.*, 1994).

6.2. Machado-Joseph disease clinical features

Machado-Joseph disease (MJD) results from a mutation in the Ataxin-3 gene (*ATXN3*), with a CAG pathogenic repeat length above 55. The mutated protein inclusions are found in the nucleus of neurons located mainly in cerebellar dentate nuclei, basal ganglia, brain stem, striatum and spinal cord (Koeppen, 2005; Alves *et al.*, 2008; Bettencourt *et al.*, 2011).

The clinical manifestations often include clumsiness and weakness in the arms and legs, spasticity, speech and swallowing difficulties, involuntary eye movements and double vision, which can be easily mistaken with drunkenness. Dystonia is also a common symptom, with abnormal posture, rigidity and repetitive moments that can be confounded with those of Parkinson's disease. It eventually leads to paralysis but intellectual functions remains almost intact (National Institute of Neurological Disorders and Stroke, 2011). Death generally occurs from respiratory complications, from 6 to 30 years after onset, depending on disease severity. Typically it begins in mid-30s to 50 years of age and the diagnosis can be made by a genetic test, medical history and symptoms recognition, as well as neurological and laboratory tests (Matilla-Dueñas, 2012).

6.3. General pathophysiology of polyglutamine diseases

All polyglutamine diseases share common elements of pathogenesis and some of them, including HD and MJD, seem linked to proteolytic cleavage that liberates toxic polyglutamine-containing fragments. Furthermore, the expanded proteins are prone to aggregation, facilitating the transition to a toxic conformation (Nagai *et al.*, 2007). It is highly probable that this toxicity could induce alterations in transcription, metabolism or impairment in stress response pathways. In a more detailed way, interactions of mutated protein with specific transcription factors may disturb gene expression and thus initiate neuronal loss. Also, it seems to exist a direct link between the presence of mutated protein and mitochondrial dysfunction (Lin *et al.*, 2006), as well as metabolic defects (Grafton *et al.*, 1992). Moreover, the brain seems very susceptible to protein misfolding and protein quality control mechanisms appear to decline with age. Impairments in autophagy or the ubiquitin proteasome system could derive from age and additionally from sequestering of important elements from this machinery, as chaperones, by aggregated mutated proteins itself, compromising the stress response ability of neuronal cells (Cowan *et al.*, 2003).

6.4. Current status for CSF biomarkers in HD and MJD

Unlike the diseases described above, HD and MJD present different challenges for biomarkers, since they have a known cause and the diagnostic is based on a genetic test. However, it is also crucial to define not only the onset of these diseases, but also accurately track its progress, independently of the symptomatic effects from drugs (O'Keeffe *et al.*, 2009). Some changes have been reported in CSF of patients suffering from HD and MJD, however, none has been studied systematically enough (Hersch *et al.* 2011). The most relevant studies for these diseases are summarized in Table 5.

Table 5. Candidate CSF biomarkers for Huntington's and Machado Joseph disease

Biomarker	Function	Findings	n (disease/control)	References
Huntington's disease				
Leptin	Metabolic hormone	↔	15/20	Popovic *et al.* 2004
Ghrelin	Metabolic hormone	↔	15/20	Popovic *et al.* 2004
CART	Energy homeostasis	↑	39/28	Björkqvist *et al.* 2007
Orexin A	Metabolic hormone	↔	10/10	Gaus *et al.* 2005
		↔	10/12	Meier *et al.* 2005
		↔	37/30	Björkqvist *et al.* 2006
Lactate	Anaerobic metabolism	↔	11/12	Nicoli *et al.* 1993
		↓	7/20	Gårseth *et al.* 2000
Citrate	Metabolism	↔	11/12	Nicoli *et al.* 1993
		↓	7/20	Gårseth *et al.* 2000
Pyruvate	Metabolism	↑	11/12	Nicoli *et al.* 1993
Glycine	Metabolism	↑	11/12	Nicoli *et al.* 1993
Glutamate	Metabolism	↓	6/10	Kim *et al.* 1980
		↔	11/12	Nicoli *et al.* 1993
Nitrate	NO transformation	↔	33/16	Milstien *et al.* 1994
		↑	23/41	Boll et al. 2008
SOD-1	Detoxification	↓	23/41	Boll et al. 2008
Ceruloplasmin	Iron metabolism	↓	23/41	Boll et al. 2008
Clusterin	Apoptosis	↑	20/9	Dalrymple *et al.* 2007
NfL	Axonal structure	↑	35/35	Constantinescu *et al.*
Homovalinic acid	Catecholamine metabolite	↓	15/-	Caraceni et al., 1977
		↓	8/23	Hayden et al., 1977
		↔	51/4	Kurlan *et al.* 1988
		↔	11/12	Garret *et al.* 1992
		↓	20/15	Garcia Ruiz *et al.* 1995
GABA	Neurotransmitter	↓	7/9	Glaeser *et al.* 1975
		↓	19/26	Enna *et al.* 1977
		↓	28/5	Manyam *et al.* 1978
		↓	15/19	Manyam *et al.* 1980
		↓	28/30	Uhlhaas *et al.* 1986
		↑	14/19	Bonnet *et al.* 1987

		↔	11/12	Nicoli *et al.* 1993
Choline	Metabolite	↔	15/10	Welsch *et al.* 1976
		↔	14/13	Consolo *et al.* 1977

Table 5 *(continued)*. Candidate CSF biomarkers for Huntington's and Machado Joseph disease

Biomarker	Function	Findings	n (disease/control)	References
Choline	Metabolite	↔	5/22	Flentge *et al.* 1984
		↓	6/9	Manyam *et al.* 1990a
AChE	Neurotransmitter	↔	5/8	Davis *et al.* 1979
		↓	10/19	Ruberg *et al.* 1987
		↔	6/9	Manyam *et al.* 1990a
CRF	Stress response	↑	56/21	Kurlan *et al.* 1988a
F2	Lipid peroxidation	↑	20/23	Montine *et al.* 1999a
Machado Joseph disease				
Substance P	Neuropeptide	↓	7/14	Matsuishi *et al.* 1996a
Lactate	Metabolism	↑	7/7	Matsuishi *et al.* 1996b
Pyruvate	Anaerobic metabolism	↓	7/7	Matsuishi *et al.* 1996b

↑ increased; ↓ decreased; ↔ no significant alterations; Control refers to healthy subjects.

CART: Cocaine and amphetamine regulated transcript; NfL: Neurofilament light chain; *GABA*: gamma-Aminobutyric acid; *AChE*: acetylcholinesterase; *CRF*: Corticotropin releasing factor.

The markers studied so far are mostly related with neurodegeneration general mechanisms, lacking specificity and reproducibility. Moreover, there is a scarcity of longitudinal studies for evaluation and validation of the proposed markers (Wild *et al.*, 2008). For these diseases, and since the main goal is to monitor disease progression and developing effective therapies, it is more likely that a multiple biomarker or multiple analytes approach could be more successful. It is also probable that, in the future, measurements of mutant polyglutamine proteins in biological fluids could be used as a standard in clinical trials for polyglutamine diseases (Scahill *et al.*, 2012). Some researchers pointed that endocrine function might be disrupted in Huntington's and weight loss is seen in many patients. However, the results for biomarkers in these pathways (e.g. leptin, ghrelin, CART, orexin) are inconclusive so far (Popovic *et al.*, 2004). The same is true to several biomarkers of mitochondrial dysfunction and increased oxidative stress. Other studies focus on neurotransmitter systems, particularly on GABAergic, but data interpretation is still not consensual, regardless of the main tendency seem to be a decrease in CSF levels (Weir *et al.*, 2011). For MJD, studies are even rarer with only 2 reports in CSF for substance P, lactate and pyruvate. Some authors refer S100b and neuron-specific enolase (NSE) as possible biomarker candidates in blood, but data is inconsistent as well (Tort *et al.*, 2005; Zhou *et al.*, 2011).

7. Highlights and concluding remarks

Biomarkers for neurodegenerative diseases are an urgent need, mostly giving the raise and prevalence of these disorders, the difficulties in diagnostic and the absence of disease-modifying therapeutics (Kieburtz *et al*., 2007). In the last decade, a very large number of candidate biomarkers have been studied and investigated. Although these efforts and the developments in molecular and imaging techniques, there are no validated markers in clinical practice so far, with the exception of $A\beta_{42}$ and tau protein measurements in CSF for Alzheimer's disease. It is expected that this scenario will change in the next few years, primarily for Parkinson's disease (Noelker *et al.* 2011). Nevertheless, some biomarkers already proposed are reaching an important role in management of these diseases and in the planning of clinical trials, a tendency that will continue to growth in the future (Gonzalez-Cuyar *et al*., 2011).

Regardless of the practicability and simplicity of blood-based biomarkers, so far results for this body fluid have not been reproducible, and results from diverse groups are significantly different. This limitation has been more easily overcome in CSF biomarkers. Due to its proximity to the brain tissue, CSF reflects more accurately brain metabolism, either in health or in disease. It is accessible by lumbar puncture, a procedure that, despite not as straightforward as for blood, is also safe, relatively simple and cost-effective (Mattson *et al.* 2011).

One of the major problems to overtake for the success in CSF biomarker research is the variability between studies, probably due to variations between techniques and procedures. Differences in sample collection and handling or in assay kits and protocols must be minimized by standard operation rules, preferentially as part of international programs and task forces (Bjerke et al., 2010). These joint initiatives also allow the collection of a large number of samples, in a multicenter perspective. Some examples of those initiatives are the EU Joint Programme for Neurodegenerative Disease Research, the Parkinson Progression Marker Initiative and the Alzheimer's Disease Neuroimaging Initiative, among others.

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