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Review

Diagnostic cerebrospinal fluid biomarkers for Parkinson's disease: A pathogenetically based approach

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ABSTRACT

The inaccuracy of the early diagnosis of Parkinson's disease (PD) has been a major incentive for studies aimed at the identification of biomarkers. Brain-derived cerebrospinal fluid (CSF) proteins are potential biomarkers considering the major role that proteins play in PD pathogenesis. In this review, we discuss the current hypotheses about the pathogenesis of PD and identify the most promising candidate biomarkers among the CSF proteins studied so far. The list of potential markers includes proteins involved in various pathogenetic processes, such as oxidative stress and protein aggregation. This list will undoubtedly grow in the near future by application of CSF proteomics and subsequent validation of identified proteins. Probably a single biomarker will not suffice to reach high sensitivity and specificity, because PD is pathogenetically heterogeneous and shares etiological factors with other neurodegenerative diseases. Furthermore, identified candidate biomarkers will have to be thoroughly validated before they can be implemented as diagnostic aids.

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The need for biomarkers in Parkinson's disease

The diagnosis of Parkinson's disease (PD) is currently mainly based on clinical features (Tolosa et al., 2006), i.e. the presence of bradykinesia in combination with muscle rigidity, resting tremor or postural instability, the absence of symptoms that indicate atypical parkinsonian disorders and supporting findings including a positive effect of dopaminergic medication (Hughes et al., 1992). Despite these clear criteria, diagnosing PD can be difficult, especially in its early stages. In particular, essential tremor and atypical parkinsonian syndromes such as progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) may initially mimic PD. The positive predictive value of the final clinical diagnosis of idiopathic PD made by movement disorder specialists was demonstrated to be very high, 98.6% (Hughes et al., 2002). However, in the same study, almost one third of the clinical diagnoses in patients with parkinsonism had been revised in on average the first five years of the disease (Hughes et al., 2002). Diagnostic accuracy in the early stages of the disease is important for the patient and, moreover, facilitates evaluation of future neuroprotective therapies. To improve the accuracy of the early diagnosis of PD, biomarkers are urgently needed. Biomarkers can be defined as characteristics that are objectively measured as indicators of normal and pathogenetic processes or responses to a therapeutic intervention. Examples of biomarkers for PD are imaging markers such as striatal dopamine transporter binding measured using single photon emission computed tomography (DaT-SPECT) or clinical markers of disease including measurement of non-motor functions such as sense of smell or autonomic function. Proteins in csf and/or blood may also serve as biomarkers for PD, but are not yet used in clinical practice. Ideally, biomarkers should be sensitive, reproducible, closely associated with the disease process, easy to measure, inexpensive, non-invasive and thoroughly validated (Michell et al., 2004). Biomarkers fulfilling all of these criteria have not yet been identified for PD.

The origin of CSF proteins and CSF physiology

Cerebrospinal fluid (CSF) is a potential source of PD biomarkers in living patients, because it is in direct contact with the diseased brain. Specific proteins play a major role in the pathogenesis of PD and brain-derived CSF proteins are therefore promising candidate biomarkers. However, the majority of the CSF proteins are believed to originate from the blood rather than directly from the surrounding brain tissue. These blood-derived proteins enter the CSF at the choroid plexus and along the flow of the CSF from the ventricles to the subarachnoid space (Huhmer et al., 2006). As a consequence, the concentration of blood-derived proteins differs between ventricular and lumbar CSF (Reiber, 1994). In addition to blood-derived proteins, brain tissue proteins contribute to the CSF pool. A recent proteomics study reported that almost 10% of identified CSF proteins overlapped with proteins detected in frontal cortex tissue of human subjects (Pan et al., 2007). Vice versa, in the same study more than 20% of the proteins detected in frontal cortex tissue were detectable in the CSF (Pan et al., 2007). Brain tissue proteins that are not detectable in CSF may either not diffuse into the CSF because they are for example membrane bound (Mogi et al., 1996a), or they may be internally recycled in brain tissue, form insoluble aggregates, or their levels may be too low to be detected (Shi et al., 2009). The total protein concentration in CSF obtained by lumbar puncture is about 200 times lower than in blood plasma (Huhmer et al., 2006) and normally varies between 150 and 500 mg/L. Because of the relatively high concentration of proteins in blood, blood contamination during lumbar puncture can have a significant effect on the CSF proteome (Hong et al., 2010). The CSF protein concentration is further influenced by the effect of circadian rhythms on the CSF secretion rate, the maximum of which at 02.00 h is 3.5 times higher than its minimum at 18.00 h (Nilsson et al., 1992). These pre-analytical factors may profoundly influence protein levels which emphasizes the importance of standardized protocols for CSF collection (Teunissen et al., 2009).

Aim

In this review, we provide an overview of CSF proteins studied in PD so far and use a pathogenetically driven approach to identify the most promising diagnostic candidate biomarkers among them. For a better understanding of the results, we first briefly review the currently leading hypotheses about PD pathogenesis and discuss the proteins that play a role in these pathogenetic processes. Promising candidate CSF biomarkers are selected based upon their relationship with the pathogenesis of PD and their different expression levels compared to controls in both CSF and brain tissue. We discuss the challenges encountered in the search for sensitive and specific biomarkers and give recommendations for future biomarker studies.

Search strategy

A PUBMED search was done up to March 2010, for ("Parkinsonian Disorders"[Mesh] OR Parkinson*) AND ("Proteins"[Mesh] OR "Enzymes and Coenzymes"[Mesh] OR "Biological markers"[Mesh]) AND ("Cerebrospinal Fluid"[Mesh] OR "cerebrospinal fluid"[subheading]). In addition, protein names were entered as free terms. This resulted in 712 hits. Only papers in English concerning human subjects were included and only studies dealing with a comparison between a PD group of at least 10 patients and a control group were considered. For proteomic studies, differently expressed proteins had to be validated in individual samples. Only studies using lumbar CSF were used, excluding studies on ventricular or post-mortem CSF, because of the different protein composition of ventricular CSF compared to lumbar CSF (Reiber, 1994) and degradation of proteins due to post-mortem delay, respectively. In total, 141 papers fulfilled the criteria. Proteins included in these studies were classified according to their expected function or their relationship to PD pathogenesis. Several proteins had multiple alleged roles and could be assigned to multiple groups. Therefore, we simplified the classification by assigning proteins to the group of their expected main contribution or relationship to PD pathogenesis.

Main hypotheses about PD pathogenesis (Fig. 1)

Pathologically, PD is characterized by the presence of Lewy bodies and Lewy neurites as well as the loss of catecholaminergic neurons in the substantia nigra and locus ceruleus. The Lewy bodies contain a large variety of aggregated proteins, including α-synuclein and ubiquitin. Post-mortem studies and the identification of gene mutations associated with parkinsonism, have led to increased insight in the processes and proteins that play a role in PD pathogenesis. These processes will be summarized in the following paragraphs.

Mitochondrial dysfunction and increased oxidative stress

Already in the eighties and nineties of the 20th century, mitochondrial dysfunction was implicated in PD pathogenesis through a reduction of mitochondrial complex I activity in the substantia nigra of PD patients compared to controls (Schapira et al., 1989). The realisation that a metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which exhibits its effect by interference in the mitochondrial electron transport chain by inhibiting mitochondrial complex I (Tipton and Singer, 1993), could cause parkinsonism and the development of an MPTP animal model for PD further stressed the role of mitochondrial dysfunction. Mitochondrial complex I was also shown to be inhibited by the pesticide rotenone. Chronic exposure to this pesticide can result in symptoms that resemble Parkinson's disease (Betarbet et al., 2000). Furthermore, altered levels of the mitochondria-related proteins prohibitin, ATP synthase and superoxide dismutase 2 (SOD2) were demonstrated in the substantia nigra and frontal cortex tissue of PD patients compared to controls (Ferrer et al., 2007). Moreover, the protein products of many genes associated with monogenetic forms of parkinsonism, including α-synuclein, Parkin, DJ-1, PINK1, LRRK2 and HTRA2, have been implicated in mitochondrial dysfunction and/or oxidative stress (Lin and Beal, 2006). Loss of mitochondrial function is likely to play a major role in apoptosis-mediated cell death via release of pro-apoptotic proteins like cytochrome C, second messenger of mitochondrial activator of caspases (SMAC) and HTRA2 (Lin and Beal, 2006), and reduced ATP formation by oxidative phosphorylation. Moreover, dysfunction of mitochondria leads to an increase in oxygen free radicals and, consequently, increased oxidative stress (Schapira, 2008). Indeed, in the substantia nigra of PD patients increased amounts of oxidatively modified proteins have been observed, such as oxidatively modified UCH-L1 (Choi et al., 2004) and nitrated α-synuclein (Giasson et al., 2000). In addition to increased levels of oxidatively modified proteins, alterations in antioxidant protective systems, most notably reduced levels of the antioxidant glutathione (GSH) have been identified in the substantia nigra of PD patients compared to controls (Sian et al., 1994).

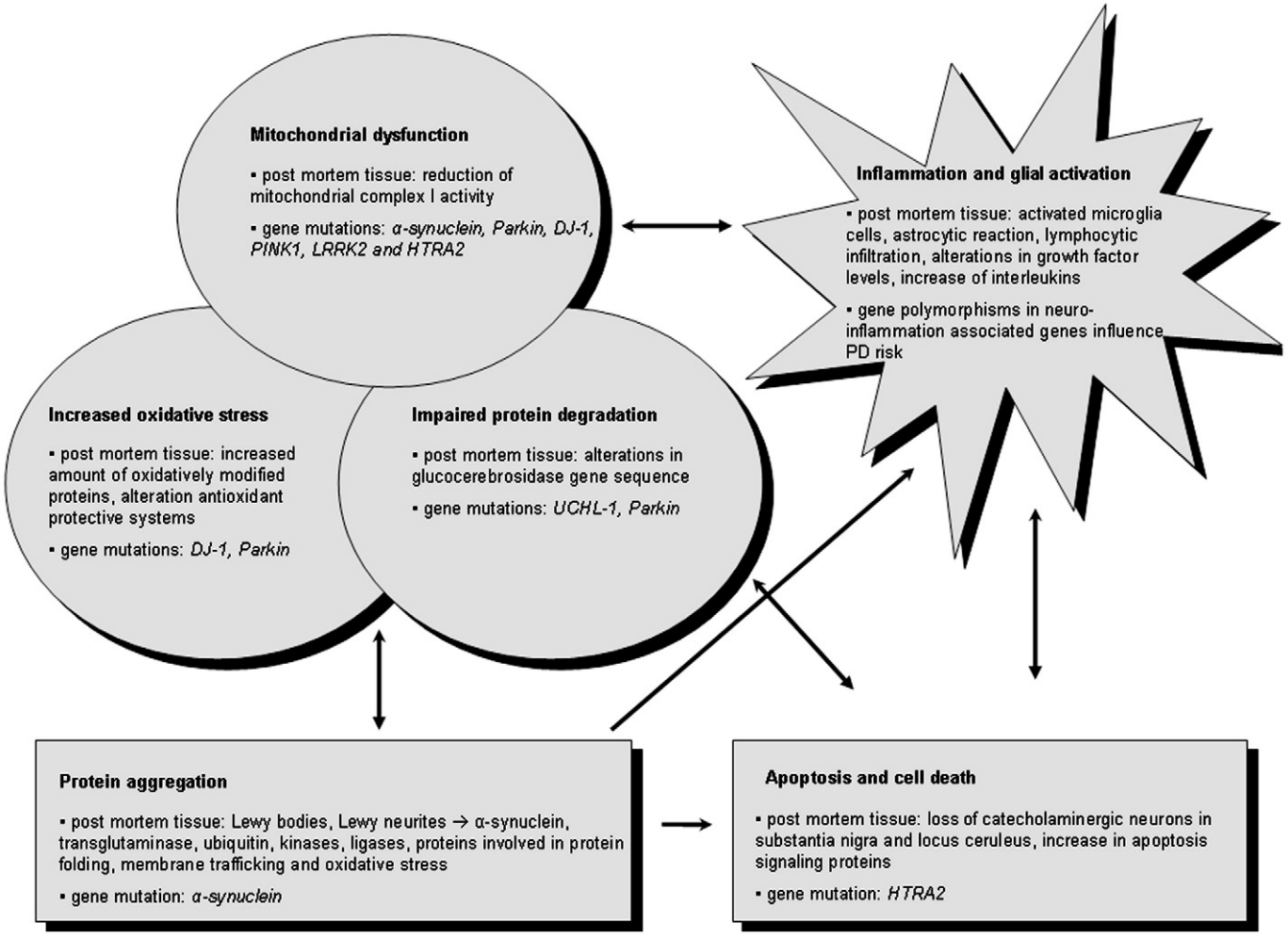

Fig. 1. Main hypotheses about PD pathogenesis based on current literature involve mitochondrial dysfunction, increased oxidative stress, impaired protein degradation, protein aggregation, inflammation and glial activation, apoptosis and cell death and their interactions. The post-mortem findings and gene mutations associated with parkinsonism that support these hypotheses are shown in this figure.

Impaired protein degradation

Impairments in protein degradation systems have also been implicated in the pathogenesis of PD. These systems, including the lysosomal degradation pathway and the ubiquitin–proteasome system, are involved in the degradation of misfolded, mutant, denatured or otherwise damaged proteins (Betarbet et al., 2005). The lysosomal degradation pathway is for example concerned with the degradation of oligomeric intermediates of α-synuclein (Lee et al., 2004). These oligomeric intermediates are considered the toxic forms of α-synuclein, which cause cellular dysfunction and cell death (El-Agnaf et al., 2003).

Involvement of the lysosomal degradation pathway in the pathogenesis of PD is supported by alterations in the glucocerebrosidase gene sequence, a lysosomal enzyme, in post-mortem brain tissue of PD patients (Lwin et al., 2004). Twelve out of 57 PD patients had mutations in this gene, compared to none of 44 control subjects. Mutations in the ubiquitin–proteasome system, a system that labels proteins with ubiquitin and guides them to the proteasome for degradation, can also result in parkinsonism (Schapira, 2008). The ubiquitin dependent proteolytic pathway is affected in patients with a mutation in the ubiquitin carboxyl-terminal esterase L1 (UCH-L1) gene, a mutation reported in two German siblings (Leroy et al., 1998), and in patients with Parkin mutations that accounts for almost 50% of familial young-onset PD (Lucking et al., 2000).

Protein aggregation and Lewy body formation

The production of misfolded, mutant, denatured or otherwise damaged proteins and their impaired degradation results in the accumulation and aggregation of proteins and the formation of Lewy bodies and Lewy neurites. A highly prevalent protein in Lewy type pathology is α-synuclein, a protein that is normally present in the presynaptic terminals of most neurons. Point mutations, duplications and triplications of the α-synuclein gene are associated with hereditary forms of PD (Polymeropoulos et al., 1997; Kruger et al., 1998; Zarranz et al., 2004; Chartier-Harlin et al., 2004; Singleton et al., 2003). α-Synuclein is present in its monomeric form, although trimers may also be present in physiological conditions (Leng et al., 2001). In PD and other synucleinopathies, monomeric α-synuclein aggregates into insoluble fibrils. Intermediate stages in the formation of these aggregates are soluble oligomers and the subsequently formed α-synuclein protofibrils (El-Agnaf et al., 2003). These intermediates are considered to be the toxic forms of α-synuclein (El-Agnaf et al., 2003; Schapira, 2006; Kazantsev and Kolchinsky, 2008). Several factors facilitate fibril formation and subsequent aggregation, for example point mutations in the α-synuclein gene, phosphorylation of α-synuclein at Ser129, a decrease in pH, an increase in temperature or the presence of metal ions and other small charged molecules (reviewed in Uversky (2007)). In addition, the aggregation of α-synuclein can be induced by the protein tissue transglutaminase. Tissue transglutaminase may contribute to the formation of Lewy bodies by crosslinking α-synuclein proteins (Junn et al., 2003). A recent proteomic analysis revealed that in addition to α-synuclein, many other proteins are present in Lewy bodies, including several kinases, ligases and proteins involved in protein folding, membrane trafficking and oxidative stress (Xia et al., 2008).

Inflammation and glial activation

In the substantia nigra of PD patients inflammation has repeatedly been demonstrated, comprising microglial activation, astrogliosis and lymphocytic infiltration (Hirsch and Hunot, 2009). Increased levels of interleukins (Mogi et al., 1994a) and alterations in growth factor levels (Mogi et al., 1999; Parain et al., 1999; Mogi et al., 1994a) in the substantia nigra and striatum of PD patients are molecular indicators of inflammation and glial involvement. It is hypothesized that the inflammatory changes contribute to the cascade of events leading to neurodegeneration and hence disease progression (Hirsch and Hunot, 2009). However, inflammation may also be a response to the neurodegenerative process. Supportive of a contributory role of inflammation in PD pathogenesis is the relationship between polymorphisms in neuro-inflammation associated genes, such as tumor necrosis factor-alpha (TNF-α), interleukin-1-beta and interleukin-6, and the risk of PD (Hirsch and Hunot, 2009) as well as the protective effect of non-steroidal anti inflammatory drugs (NSAIDs) (Chen et al., 2003). However, neuro-inflammatory processes are not specific for PD, but are also observed in other neurodegenerative disorders associated with parkinsonism, such as PSP and MSA (McGeer and McGeer, 2004; Sakurai et al., 2002).

Apoptosis and cell death

Apoptosis-mediated cell death has also been put forward as a possible pathogenetic factor in PD. Mochizuki et al. histochemically detected apoptosis in the midbrain of 8 out of 11 PD patients compared to 1 out of 6 control subjects (Mochizuki et al., 1996). Furthermore, the concentration of anti-apoptotic protein bcl-2 (Yuan and Yankner, 2000) was compensatorily increased in nigrostriatal dopaminergic neurons in PD patients compared to controls (Mogi et al., 1996a). Also soluble Fas, an apoptosis-signaling receptor molecule, and Annexin V, which plays a role in apoptotic cell death and necrosis, were increased in the substantia nigra in PD suggesting a role for apoptosis in PD pathogenesis (Mogi et al., 1996b; Werner et al., 2008). The fact that mutations in the apoptosis related HTRA2 gene were demonstrated in PD patients (Strauss et al., 2005) further strengthens the likelihood of involvement of apoptosis in the pathogenesis of PD. The HTRA2 gene encodes serine protease, a mitochondrial protein that degrades apoptosis inhibitors inside mitochondria, and promotes apoptosis in the cytosol (Lin and Beal, 2006).

CSF proteins reflecting PD pathogenesis (Table 1)

Mitochondrial dysfunction and oxidative stress

Studies investigating CSF levels of the mitochondria-related antioxidant DJ-1 have yielded conflicting results. Waragai et al. reported increased levels of DJ-1 in PD patients compared to non-PD controls, especially in the early stages of PD (Waragai et al., 2006). A more recent study however reported decreased DJ-1 levels in CSF of PD patients compared to Alzheimer's disease patients and controls. The discrepancy between the results of the two studies was ascribed to either cross-reactive molecules detected by the ELISA technique, limitations of the ELISA kit itself, or the degree of blood contamination (Hong et al., 2010). Changes in the levels of oxidative stress related proteins have also been demonstrated in the CSF of PD patients. For example the concentration of nitrated manganese superoxide dismutase (Mn-SOD), an assumed marker for peroxynitrite-mediated oxidative stress was increased in a group of 10 PD patients compared to controls (Aoyama et al., 2000).

The antioxidant activity of the Cu/Zn-dependent superoxide dismutase (SOD1) was reduced in the CSF of PD, Alzheimer's disease (AD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) patients (Boll et al., 2008). Oxidatively modified forms of this same protein were increased the CSF of PD patients compared to controls (Guo et al., 2009). Ceruloplasmin and transferrin are other antioxidant proteins studied in CSF (Abdi et al., 2006; Boll et al., 1999; Loeffler et al., 1994; van Kamp et al., 1995; Boll et al., 2008). The ferroxidase enzyme in ceruloplasmin converts $Fe2+$ into $Fe3+$ that is transported by transferrin. Together they limit the $Fe2+$-catalyzed generation of toxic hydroxyl radicals (Loeffler et al., 1994). CSF transferrin levels in PD patients did not differ from the CSF levels in controls (Loeffler et al., 1994; van Kamp et al., 1995), but ferroxidase activity and CSF ceruloplasmin levels were reduced

Table 1
Studied CSF proteins in PD patients compared to controls that reflect PD pathogenesis.

Mitochondrial dysfunction and oxidative stress	
Nitrated manganese superoxide dismutase (Mn-SOD)	↑ (Aoyama et al., 2000)
Oxidatively modified SOD1	↑ (Guo et al., 2009)
Cu/Zn-dependent SOD1 activity	↓ (Boll et al., 2008)
SOD activity	= (De Deyn et al., 1998; Marttila et al., 1988)
Serum transferrin N-terminal lobe	↑ (Sinha et al., 2009)
DJ-1	↑ (Waragai et al., 2006); ↓ (Hong et al., 2010)
Glutathione	= (Konings et al., 1999; Marttila et al., 1988)
Glutathione peroxidase activity	= (Marttila et al., 1988)
Ceruloplasmin (ferroxidase)	↓ (Abdi et al., 2006); = (Loeffler et al., 1994)
Ferroxidase activity	↓ (Boll et al., 1999, 2008)
Ferritin	= (Dexter et al., 1990; Kuiper et al., 1994; Pall et al., 1990)
Transferrin	= (Loeffler et al., 1994; van Kamp et al., 1995)
Haptoglobin	↑ (Abdi et al., 2006)
Protein degradation	
Beta-glucocerebrosidase activity	↓ (Balducci et al., 2007)
Alpha-mannosidase activity	↓ (Balducci et al., 2007)
Beta-mannosidase activity	↓ (Balducci et al., 2007)
Beta-hexoaminidase activity	= (Balducci et al., 2007)
Beta-galactosidase activity	= (Balducci et al., 2007)
Lewy body associated proteins	
α-Synuclein	= (Borghi et al., 2000; Ohrfelt et al., 2009); ↓ (Tokuda et al., 2006; Hong et al., 2010)
Tissue transglutaminase	↑ (Vermes et al., 2004)
Neurofilament heavy chain (NFH-SMI35)	= (Brettschneider et al., 2006)
Phosphorylated neurofilament heavy chain (NFHp35)	= (Abdo et al., 2007)
Neurofilament light chain (NFL)	= (Abdo et al., 2007; Holmberg et al., 1998; Constantinescu et al., 2010)
Osteopontin	↑ (Maetzler et al., 2007)
Inflammation and glial activation	
Interleukins	
Interleukin-1-beta	= (Pirttila et al., 1994); ↑ (Blum-Degen et al., 1995); not detectable (Mogi and Nagatsu, 1999)
Interleukin-2	= (Blum-Degen et al., 1995); not detectable (Mogi and Nagatsu, 1999)
Interleukin-4	Not detectable (Mogi and Nagatsu, 1999)
Interleukin-6	↑ (Blum-Degen et al., 1995; Muller et al., 1998); not detectable (Mogi and Nagatsu, 1999)
Interleukin-8	↑ (Zhang et al., 2008)
Interleukin-10	= (Rota et al., 2006)
Interleukin-12	= (Rota et al., 2006)
Growth factors	
Brain-derived neurotrophic factor (BDNF)	↓ (Zhang et al., 2008); ↑ (Salehi, Mashayekhi, 2009)
Growth associated protein (GAP-43)	↓ (Sjogren et al., 2000)
Vascular endothelial growth factor	= (Nagata et al., 2007)
Striatal derived neurotrophic factor (not further specified)	↑ (Carvey et al., 1991)
Transforming growth factor-beta1 (TGF-beta1)	= (Rota et al., 2006); not detectable (Mogi and Nagatsu, 1999)
Basic fibroblast growth factor (bFGF)	Not detectable (Mogi and Nagatsu, 1999)
Transforming growth factor-alpha (TGF-α)	Not detectable (Mogi and Nagatsu, 1999)
Epidermal growth factor (EGF)	Not detectable (Mogi and Nagatsu, 1999)
Insulin-like growth factor-1 (IGF-1)	↑ (Mashayekhi et al., 2010)
Insulin-like growth factor binding proteins (IGFBPs)	↑ (Mashayekhi et al., 2010)
Complement system	
Complement protein C3b	↓ (Finehout et al., 2005)
Complement protein C4alpha	↓ (Guo et al., 2009)
Complement protein C4b	↓ (Finehout et al., 2005)
Complement protein C4d	= (Yamada et al., 1994)
Factor B (complement factor B)	↓ (Finehout et al., 2005)
Factor H (complement factor H)	= (Finehout et al., 2005)
Circulation immune complex (CIC) to C1q	= (Yamada et al., 1994)
Antibodies	
Antibodies to arboviruses	Not detectable (Elizan et al., 1978)
Antibodies to measles virus	↑ (Marttila et al., 1982)
Antibodies to HSV	↑ (Marttila et al., 1982)
Antibodies to HSV1	= (Elizan et al., 1979); slightly detectable (Marttila et al., 1981)
Antibodies to HSV2	= (Elizan et al., 1979); slightly detectable (Marttila et al., 1981)
Antibodies to CMV	= (Elizan et al., 1979); slightly detectable (Marttila et al., 1981)
Antibodies to coronavirus	↑ (Fazzini et al., 1992)
Antibodies to hsp 65	↑ (Fiszer et al., 1996)
Antibodies to hsp 70	↑ (Fiszer et al., 1996)
CSF antibodies reacting with structures of rat pons/medulla	= (Imrich et al., 2006)
IgG immunoreactive to rat brain tissue neuronal cell bodies in SN and ventral tegmental region	↑ (Carvey et al., 1991)
IgG	= (Haussermann et al., 2001)
IgG index	= (Haussermann et al., 2001)
Oligoclonal bands	= (Haussermann et al., 2001)

(continued on next page)

Table 1 (*continued*)

Inflammation and glial activation	
Unclassified immune system or glial proteins	
Glial fibrillary acidic protein (GFAP)	= (Holmberg et al., 1998; Constantinescu et al., 2010)
Matrix metalloproteinase (MMP)-2 (indirectly related to immune system)	= (Lorenzl et al., 2003)
Matrix metalloproteinase (MMP)-9 (indirectly related to immune system)	= (Lorenzl et al., 2003)
Tissue inhibitor of MMP 1 (TIMP-1) (indirectly related to immune system)	↑ (Lorenzl et al., 2003)
Tissue inhibitor of MMP 2 (TIMP-2) (indirectly related to immune system)	= (Lorenzl et al., 2003)
CSF/serum ratio for albumin (indirectly related to immune system)	= (Haussermann et al., 2001)
Beta-fibrinogen (indirectly related to immune system)	= (Abdi et al., 2006)
Ulinastatin-like immunoreactive substance (UTIRS)	= (Shikimi et al., 1997)
Monocyte chemotactic protein-1	↑ (Nagata et al., 2007)
Interferon-gamma (IFN-gamma)	= (Rota et al., 2006)
Tumor necrosis factor-alpha (TNF-α)	↑ (Le et al., 1999; Mogi and Nagatsu, 1999)
Beta-2-microglobulin	↓ (Mogi et al., 1989); ↑ (Zhang et al., 2008); not detectable (Mogi and Nagatsu, 1999)
Alpha-1-antichymotrypsin	= (Pirttila et al., 1994)
Apoptosis and cell death	
Soluble form of Fas (sFas)	Not detectable (Mogi et al., 1996b)
Bcl-2	Not detectable (Mogi et al., 1996a)
Annexin V	↓ (Vermes et al., 1999)

Note that the classification of proteins into groups is simplified; several proteins are involved in multiple pathways and can be assigned to multiple groups. ↑ indicates elevated levels in PD compared to control patients; ↓ indicates decreased levels in PD compared to control patients; = indicates no difference between PD and control patients.

in PD (Boll et al., 1999, 2008) (ceruloplasmin: sensitivity of 0.556 at 95% specificity of ROC curve; area under ROC curve 0.809 (Abdi et al., 2006)).

Impaired protein degradation

In CSF of PD patients, the activities of three out of five studied lysosomal enzymes were reduced with 24–71%: α-mannosidase ($p<0.01$), β-mannosidase ($0.05>p>0.01$) and β-glucocerebrosidase ($0.05>p>0.01$) (Balducci et al., 2007). To the best of our knowledge, none of the proteins that are directly involved in the ubiquitin–proteasome system has been studied in CSF for PD biomarker purposes.

Protein aggregation and Lewy body formation

Alpha-synuclein, the main component of Lewy bodies, is detectable in both CSF and blood. Most applied ELISAs have detected total α-synuclein (Borghi et al., 2000; Lee et al., 2004; Li et al., 2007; Mollenhauer et al., 2008; Ohrfelt et al., 2009; Tokuda et al., 2006; Hong et al., 2010), but for plasma, and more recently for CSF, a specific ELISA for its oligomeric forms has been developed (El-Agnaf et al., 2006; Maetzler et al., 2009c). This oligomeric form of α-synuclein was increased in CSF of patients with Lewy body disease (PD and DLB combined) compared to non-Lewy body disease subjects (controls and tauopathies) (Maetzler et al., 2009c). However, these results have not been included in our Table 1, because levels of oligomeric α-synuclein of the PD patients were not reported separately by Maetzler et al. Total α-synuclein in CSF was either decreased (Tokuda et al., 2006; Mollenhauer et al., 2008; Hong et al., 2010) or unchanged (Borghi et al., 2000; Ohrfelt et al., 2009) in PD patients compared to controls. The largest study on CSF levels of α-synuclein was recently published by Hong et al. who observed reduced levels of α-synuclein in 117 PD patients compared to both 50 Alzheimer's disease patients and 132 controls after controlling for blood contamination (Hong et al., 2010). No association between α-synuclein levels and disease severity was found in this study, in contrast to the results of a previous study that showed an inverse correlation between α-synuclein and disease severity (Tokuda et al., 2006).

Tissue transglutaminase, which may contribute to α-synuclein aggregation by promoting crosslinks (Junn et al., 2003) was increased almost tenfold in PD patients in comparison to controls ($p=0.001$), although the overlap between controls and certain PD patients indicated low sensitivity of this potential diagnostic marker (Vermes et al., 2004). Osteopontin levels, one of several other proteins expressed in Lewy bodies, were also increased in CSF of PD patients compared to controls (Maetzler et al., 2007). This protein may be involved in many pathogenetic mechanisms including oxidative stress, mitochondrial impairment, apoptosis and cytokine regulation. Other proteins that have been detected in Lewy bodies are neurofilaments (Hill et al., 1991) that are part of the cytoskeleton. Levels of both neurofilament heavy chain and light isoforms were similar in the CSF of PD patients compared to controls (Abdo et al., 2007; Brettschneider et al., 2006; Holmberg et al., 1998). However, neurofilament levels were increased in CSF of PSP and MSA patients compared to PD patients, an observation that has been interpreted to reflect the progressive nature of the disease process in these diseases (Abdo et al., 2007; Brettschneider et al., 2006; Holmberg et al., 1998).

Inflammation and glial activation

The involvement of inflammatory mechanisms in PD is supported by increased CSF levels of interleukins, including interleukin-1-beta, interleukin-6 and interleukin-8 (Blum-Degen et al., 1995; Muller et al., 1998; Zhang et al., 2008) and decreased levels of components of the complement system (complement protein C3b, C4alpha, C4b and factor B) (Finehout et al., 2005; Guo et al., 2009) in PD patients. These decreased levels of components of the complement system could indicate an overactivation of the complement system and subsequent depletion. Furthermore, the growth factors brain-derived neurotrophic factor (BDNF), growth associated protein (GAP-43), insulin-like growth factor-1 and striatal derived neurotrophic factor were reported to be differently expressed, although results are conflicting for BDNF (Carvey et al., 1991; Sjogren et al., 2000; Zhang et al., 2008; Salehi and Mashayekhi, 2009; Mashayekhi et al., 2010). CSF studies also linked PD to the generation of auto-antibodies and increased viral antibody levels (Fazzini et al., 1992; Gao et al., 1994; Marttila et al., 1982), although intrathecal antibody production could not be demonstrated (Marttila et al., 1982).

Apoptosis and cell death

The apoptosis-signaling molecules sFas and bcl-2 protein, which are increased in nigrostriatal tissue of PD patients, were not detectable in CSF using a two-site sandwich enzyme-linked immunosorbent assay (Mogi et al., 1996a,b). Bcl-2 may not be detectable because it is membrane bound (Mogi et al., 1996a). CSF levels of Annexin V, which adheres to dying cells, were decreased in PD patients possibly due to increased usage (Vermes et al., 1999).

CSF proteins not related to above described PD pathogenetic mechanisms (Table 2)

Alzheimer's disease associated proteins

Alzheimer's disease-type neuropathological changes are common in PD patients (Mattila et al., 1998). The three CSF markers most studied in

Table 2
Studied CSF proteins in PD patients compared to controls that are not related to the reviewed PD pathogenetic mechanisms.

AD associated proteins	
Tau	= (Arai et al., 1997; Bibl et al., 2007; Blennow et al., 1995; Jansen et al., 1998; Kahle et al., 2000; Lins et al., 2004; Molina et al., 1997; Mollenhauer et al., 2006; Paraskevas et al., 2005; Sjogren et al., 2002, 2001, 2000; Zhang et al., 2008; Parnetti et al., 2008; Borroni et al., 2009; Kanemaru et al., 2000; Borroni et al., 2008; Compta et al., 2009); ↓ (Abdo et al., 2007), ↑ (Compta et al., 2009) (PDD)
Phospho-tau	= (Blennow et al., 1995; Lins et al., 2004; Sjogren et al., 2002, 2001; Parnetti et al., 2008; Borroni et al., 2009, 2008; Compta et al., 2009); ↑ (Compta et al., 2009) (PDD)
Beta amyloid (not further specified)	= (van Gool et al., 1995)
Beta amyloid-42	= (Holmberg et al., 2003; Lins et al., 2004; Mollenhauer et al., 2006; Sjogren et al., 2000; Verbeek et al., 2004; Zhang et al., 2008; Kanemaru et al., 2000; Compta et al., 2009); ↓ (Bibl et al., 2007; Sjogren et al., 2002; Parnetti et al., 2008; Compta et al., 2009) (PDD(Compta et al., 2009))
Beta amyloid precursor protein	↓ (Henriksson et al., 1991)
Ad7c-neuronal thread protein	= (de la Monte et al., 1992; Kahle et al., 2000; Monte et al., 1997; Yamada et al., 1993)
Aspartate-aminotransferase (ASAT)	= (Jansen et al., 1998)
ApoAII	↓ (Zhang et al., 2008)
ApoE	↓ (Zhang et al., 2008); ↑ (Guo et al., 2009)
ApoJ (clusterin)	= (Lidstrom et al., 2001)
Apolipoprotein C-I	= (Abdi et al., 2006)
Neuropeptides	
Chromogranin B (secretogranin 1) (precursor for neuropeptides)	= (Abdi et al., 2006)
Met5-enkephalin-Arg6-Gly7-Leu8 (MERGL)	↓ (Baronti et al., 1991)
Methionine-enkephalin	↓ (Yaksh et al., 1990)
Encrypted met-enkephalin	↓ (Yaksh et al., 1990)
Dynorpin A(1–8)	= (Baronti et al., 1991)
Diazepam binding inhibitor (DBI)	↑ (Ferrero et al., 1988a,b)
Beta-endorphin like immunoreactivity	= (Jolkkonen et al., 1987; Hartikainen et al., 1992); ↓ (Nappi et al., 1985)
Cholecystokinin	= (Verbanck et al., 1984)
Cholecystokinin-8 (CCK)	↓ (Lotstra et al., 1985)
Neuropeptide Y	= (Yaksh et al., 1990); ↓ (Martignoni et al., 1992)
Substance P	= (Matsuishi et al., 1999; Nutt et al., 1980)
High molecular weight form of somatostatin-like immunoreactivity (HMV-SST)	= (Strittmatter et al., 1996)
Somatostatin-like immunoreactivity	= (Hartikainen et al., 1992; Poewe et al., 1990; Volicer et al., 1986); ↑ (Espino et al., 1995); ↓ (Dupont et al., 1982; Jolkkonen et al., 1986; Strittmatter et al., 1996; Strittmatter and Cramer, 1992; Unger et al., 1988)
Somatostatin-14	= (Strittmatter et al., 1996)
Somatostatin-25/28	= (Strittmatter et al., 1996)
Des-ala-somatostatin	↑ (Strittmatter et al., 1996)
Corticotropin-releasing hormone (CRH)	= (Suemaru et al., 1995)
Arginine vasopressin	↓ (Olsson et al., 1987; Sundquist et al., 1983)
Neurokinin A	= (Galard et al., 1992)
Homocarnosine	= (Bonnet et al., 1987)
Beta-lipotropin	= (Nappi et al., 1985)
Adrenocorticotropic hormone (ACTH)	= (Nappi et al., 1985)
Unclassified proteins	
Total protein concentration	= (Zubenko et al., 1986); ↑ (Hartikainen et al., 1992)
Acetylcholinesterase immunoreactivity	= (Konings et al., 1995) (PD, non-demented); ↓ (Konings et al., 1995) (PDD)
Acetylcholinesterase activity	= (Hartikainen et al., 1992; Jolkkonen et al., 1986; Konings et al., 1995; Manyam et al., 1990; Ruberg et al., 1987; Zubenko et al., 1986); ↓ (Konings et al., 1995) (PDD)
Butyrylcholinesterase activity	= (Ruberg et al., 1987; Sirvio et al., 1987; Maetzler et al., 2009a)
Dopamine-beta-hydroxylase activity	= (Hartikainen et al., 1992)
Angiotensin-converting enzyme (ACE)	↑ (Konings et al., 1994; Zubenko et al., 1986); ↓ (Zubenko et al., 1985)
Angiotensin-converting enzyme (ACE) activity	↑ (Konings et al., 1994) (in treated PD patients); = (Konings et al., 1994) (in untreated PD patients); ↓ (Zubenko et al., 1986, 1985)
Autotaxin (ectonucleotide pyrophosphatase/phosphodiesterase 2)	↑ (Guo et al., 2009)
Pigment epithelium-derived factor (PEDF)	= (Guo et al., 2009)
Nicotinamide-N-methyltransferase (NNMT) (endogenous toxin)	↑ (Aoyama et al., 2001) (in PD patients < 66 years)
Apolipoprotein H (beta 2-glycoprotein I)	↓ (Abdi et al., 2006)
T-cadherin (H-cadherin)	= (Abdi et al., 2006)
Vitamin D binding protein (VDBP)	= (Abdi et al., 2006), ↑ (Zhang et al., 2008)
Hemoglobin-beta-fragment	↓ (Sinha et al., 2009)
Alpha-1-microglobulin-like immunoreactive substance (alpha 1 MIRS)	= (Shikimi et al., 1997)

Note that the classification of proteins into groups is simplified; several proteins are involved in multiple pathways and can be assigned to multiple groups. ↑ indicates elevated levels in PD compared to control patients; ↓ indicates decreased levels in PD compared to control patients; = indicates no difference between PD and control patients.

AD, namely tau, phosphorylated tau and beta amyloid-42, have repeatedly been studied in PD. In PD, beta amyloid-42 was incidentally found to be decreased (Bibl et al., 2007; Compta et al., 2009; Parnetti et al., 2008; Sjogren et al., 2002) but in general appeared unchanged compared to controls (Holmberg et al., 2003; Lins et al., 2004; Mollenhauer et al., 2006; Sjogren et al., 2000; Verbeek et al., 2004; Zhang et al., 2008; Kanemaru et al., 2000). Differences in CSF tau or phosphorylated tau levels between PD and controls have only been demonstrated twice (Abdo et al., 2007; Compta et al., 2009). Most other AD associated proteins were unchanged in PD (Abdi et al., 2006; de la Monte et al., 1992; Jansen et al., 1998; Kahle

et al., 2000; Monte et al., 1997; Yamada et al., 1993; Lidstrom et al., 2001), except for apoE and apoAII protein (Zhang et al., 2008; Guo et al., 2009), which were different compared to controls. Recently, Compta et al. reported that dissimilar levels of tau, phosphorylated tau and beta amyloid-42 could only be demonstrated in a subgroup of PD patients, namely patients that were diagnosed with Parkinson's disease related dementia (PDD) (Compta et al., 2009). An explanation for these findings might be that underlying AD-pathology in PDD is responsible for the different levels of AD associated proteins.

Neuropeptides

CSF neuropeptides have been studied extensively in the eighties and nineties of the last century. Neuropeptides are short polymers of amino acids secreted by neurons for interneuronal communication purposes. They may modulate receptor sensitivity and interact with other neurotransmitters (Strittmatter et al., 1996). Several neuropeptides are decreased in CSF of PD patients compared to controls, including Met-Enkephalin (Fischer, 1974; Yaksh et al., 1990), cholecystokinin-8 (Lotstra et al., 1985) and arginine vasopressin (Olsson et al., 1987; Sundquist et al., 1983). A potential explanation for this decrease is cell death of specific neurons or suppression of their secretory activity (Strittmatter et al., 1996). Cell death may on the other hand result in increased levels of neuropeptides through the release of peptides from damaged brain tissue (Espino et al., 1995). Raised CSF peptide levels have been demonstrated for diazepam binding inhibitor (DBI) (Ferrero et al., 1988a,b) and des-ala-somatostatin (Strittmatter et al., 1996). Several neuropeptides have been reported only once and the results of some neuropeptide studies led to conflicting data (Dupont et al., 1982; Espino et al., 1995; Jolkkonen et al., 1986; Strittmatter et al., 1996; Strittmatter and Cramer, 1992; Unger et al., 1988).

Potential PD candidate biomarkers (Table 3)

To identify potential PD candidate biomarkers, we chose to use the following criteria: 1) proteins should be differently expressed in PD patients compared to controls in both affected brain tissue and CSF and (2) proteins should bear a relationship to a pathogenetic mechanism involved in PD. We state that the most sensitive and specific biomarkers for PD are within this group of pathogenesis related proteins. Table 3 lists the proteins that fulfil these criteria and provides the direction of change of protein levels in CSF and affected brain tissue. The list includes the oxidative stress related proteins ceruloplasmin, DJ-1 and oxidatively modified SOD1, the lysosomal enzyme beta-glucocerebrosidase and proteins related to protein aggregation and Lewy body formation: α-synuclein, tissue transglutaminase and osteopontin. Furthermore, a number of proteins involved in inflammation and glial activation are candidate PD biomarkers: interleukin-1-beta, interleukin-6, BDNF, tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), tumor necrosis factor-alpha (TNF-α) and beta-2-microglobulin. While the direction of change for several studied proteins is the same in CSF and brain tissue, changes in opposite directions have been observed for a number of proteins, including ceruloplasmin, DJ-1 and osteopontin. This may be the result of active transport (i.e. secretion or extraction) between tissue and CSF. Conflicting results among studied CSF proteins might result from differences in the applied assays and/or the significant effect of blood contamination that was reported for CSF levels of both DJ-1 and α-synuclein (Hong et al., 2010). The list is still limited and will undoubtedly grow in the near future by the application of proteomics and the subsequent validation of identified proteins. Furthermore, additional proteins might result from the identification of new pathogenetic processes involved in PD. It is important to stress that the candidacy of a couple of the selected potential biomarkers is based on single findings. There is a strong need for validation of the potential CSF biomarkers in preferentially pathologically confirmed cohorts and, to account for inter-laboratory variability, in multiple centers.

How to reach high sensitivity and specificity

The relative contribution of each of the various mechanisms (mitochondrial dysfunction, oxidative stress, impaired protein degradation, etcetera) to the pathogenesis may vary between PD patients. This heterogeneity in the pathogenesis of PD makes it likely that a

Table 3
Biomarker candidates: proteins related to the pathogenesis of PD that are differently expressed in PD patients compared to controls in both CSF and brain tissue.

	Brain tissue	CSF
Mitochondrial dysfunction and increased oxidative stress		
Ceruloplasmin (ferroxidase)	↑ (Loeffler et al., 1996)	↓ (Abdi et al., 2006); = (Loeffler et al., 1994)
DJ-1	↓ (Kumaran et al., 2009)	↑ (Waragai et al., 2006); ↓ (Hong et al., 2010)
Oxidatively modified superoxide dismutase 1 (SOD1)	↑ (Choi et al., 2005)	↑ (Guo et al., 2009)
Impaired protein degradation		
Beta-glucocerebrosidase activity	alteration in glucocerebrosidase gene sequence (Lwin et al., 2004)	↓ (Balducci et al., 2007)
Protein aggregation and Lewy body formation		
α-Synuclein	present in Lewy bodies, = SDS-soluble α-synuclein (Tong et al., 2010)	= (Borghi et al., 2000; Ohrfelt et al., 2009); ↓ (Tokuda et al., 2006; Hong et al., 2010)
Tissue transglutaminase	↑ (Andringa et al., 2004)	↑ (Vermes et al., 2004)
Osteopontin	↓ (Iczkiewicz et al., 2006); present in Lewy bodies (Maetzler et al., 2007)	↑ (Maetzler et al., 2007)
Inflammation and glial activation		
Interleukin 1-beta	↑ (Mogi et al., 1994a)	= (Pirttila et al., 1994); ↑ (Blum-Degen et al., 1995); not detectable (Mogi and Nagatsu, 1999)
Interleukin-6	↑ (Mogi et al., 1994a)	↑ (Blum-Degen et al., 1995; Muller et al., 1998); not detectable (Mogi and Nagatsu, 1999)
Brain-derived neurotrophic factor (BDNF)	↓ (Mogi et al., 1999; Murer et al., 2001; Parain et al., 1999)	↓ (Zhang et al., 2008); ↑ (Salehi, Mashayekhi, 2009)
Tissue inhibitor of MMP 1 (TIMP-1)	↑ (Lorenzl et al., 2002)	↑ (Lorenzl et al., 2003)
Tumor necrosis factor-alpha (TNF-α)	↑ (Mogi et al., 1994b; Nagatsu et al., 2000)	↑ (Le et al., 1999; Mogi and Nagatsu, 1999)
Beta-2-microglobulin	↑ (Mogi et al., 1995)	↓ (Mogi et al., 1989); ↑ (Zhang et al., 2008); not detectable (Mogi and Nagatsu, 1999)

SDS = sodium dodecyl sulfate; ↑ indicates elevated levels in PD compared to control patients; ↓ indicates decreased levels in PD compared to control patients; = indicates no difference between PD and control patients.

combination of proteins which represent different pathogenetic processes will be needed to accomplish a sufficiently high degree of sensitivity. A combination of candidate biomarkers listed in Table 3 may be capable to reach the required sensitivity and may differentiate PD patients in an early stage of the disease from healthy individuals.

In the clinical setting, it is also essential to differentiate PD from other neurodegenerative disorders, in particular MSA and PSP in their early stages. Several of the proteins listed in Table 3 have been studied in other neurodegenerative disorders. Although the majority of these proteins have not been studied in the atypical parkinsonian syndromes PSP and MSA, it is clear that several of these proteins are not specific for PD. The lack of specificity applies to proteins associated with different pathogenetic processes, varying from increased oxidative stress to inflammation. For example, CSF levels of glucocerebrosidase activity, decreased in PD, were also decreased in dementia with Lewy bodies (DLB) patients (Parnetti et al., 2009). CSF levels of DJ-1 have not yet been evaluated in other neurodegenerative diseases. In multiple sclerosis patients, however, DJ-1 CSF levels were significantly higher in comparison to controls (Hirotani et al., 2008). Inflammatory proteins seem to be the least specific pathogenetic group. Inflammatory cytokine interleukin-1-beta levels were increased in CSF of patients with small infarcts (Sun et al., 2009) and AD (Blum-Degen et al., 1995), whereas TIMP-1 was increased in CSF of patients diagnosed with PSP, AD, Huntington's disease and amyotrophic lateral sclerosis (Lorenzl et al., 2003). In addition, IL-6, BDNF and TNF-α were increased in CSF of AD patients (Blum-Degen et al., 1995; Tarkowski et al., 1999; Zhang et al., 2008), like in PD patients.

The lack of specificity of several candidate biomarkers can be explained by the fact that neurodegenerative disorders such as PD, MSA and PSP not only overlap clinically, but also share neuropathological characteristics and hypothesized pathogenetic mechanisms. Much like PD, both MSA and PSP are neuropathologically characterized by the presence of protein aggregates. In MSA, the aggregates are principally composed of α-synuclein and are located in oligodendroglial cells (Wakabayashi et al., 1998). In PSP, hyperphosphorylated tau accumulates in neurons (Hauw et al., 1994). Proteins involved in apoptosis and antioxidant proteins such as bcl-2 and DJ-1 can also be detected postmortem in aggregates in MSA (reviewed in Wenning et al. (2008)). In PSP, as in PD, kinases, mitochondrial dysfunction and chronic inflammation may play an important role in pathogenesis (Ludolph et al., 2009).

Neuropathologically, α-synuclein immunohistochemistry is at present the gold standard to detect PD pathology. This protein could be a highly effective PD biomarker, which in theory could differentiate the synucleinopathies (PD, MSA and DLB) from tauopathies like PSP. The disappointing results with total α-synuclein until now could be related to the studied form of this protein. Quite possibly, the toxic intermediates of α-synuclein, already found to be increased in plasma of PD patients compared to controls (El-Agnaf et al., 2006), and in CSF of a combined PD/DLB group compared to non-Lewy body disease subjects (Maetzler et al., 2009c), are the most promising target.

The rate of progression of the different neurodegenerative disorders forms a second clue to the selection of specific PD biomarkers. MSA and PSP tend to progress more rapidly than PD, with higher rates of cell death and consequently increased release of cellular proteins in the CSF. For example neurofilament protein, a cytoskeletal protein that is also present in Lewy bodies (Hill et al., 1991), is increased in the CSF of MSA, PSP and corticobasal degeneration (CBD) patients compared to PD patients (Abdo et al., 2007; Brettschneider et al., 2006; Holmberg et al., 1998) and may be useful to differentiate these atypical parkinsonian disorders from PD in its early stages.

Thirdly, it is quite possible that the most specific CSF biomarkers for PD have not yet been identified. The majority of the reviewed studies are based on hypothesis driven research. We anticipate that in the coming years, proteomic analysis of the CSF, a technique that enables large-scale unbiased identification of proteins (Shi et al., 2009), will offer great opportunities for the identification of novel and specific biomarker candidates, in particular when these proteomic studies would include additional diagnostic groups such as MSA and PSP.

Multiple markers

Altogether, a combination of biomarkers will probably be required to reach sufficiently high sensitivity and specificity. We propose to select biomarkers from different pathogenetic processes to account for the pathogenetic heterogeneity of the disease (for example DJ-1, α-synuclein and TNF-α) and additional biomarkers to differentiate PD from atypical parkinsonian disorders (for example neurofilaments).

From the perspective of combining markers, a promising biomarker study with multiple markers was performed by Zhang et al. (2008). A combination of eight proteins was derived using a proteomic CSF analysis. Subsequent antibody based validation of the combination of proteins agreed with expert diagnoses in 95% of PD patients, 95% of control subjects and 75% of AD patients. In addition to CSF proteins, other biochemical markers like oxidative stress marker 8-hydroxy-2 deoxyguanosine (8-ohdg) (Gmitterova et al., 2009; Isobe et al., 2010) and non-biochemical markers like dopamine transporter single photon emission computed tomography (DaT-SPECT), MRI, olfactory testing and neuropsychological evaluation (Graeber, 2009) can be helpful to increase sensitivity and specificity.

Finally, biomarkers that may improve the accuracy of an early PD diagnosis may also be suitable to effectively monitor disease progression. These markers of disease progression can be crucial for the evaluation of neuromodulatory or neuroprotective therapies (Maetzler et al., 2009b). Studies with follow-up measurements, such as the recently published study by Constantinescu et al. (2010), will be required for this purpose.

Conclusions and future directions

Changes in the levels of several of the studied CSF proteins in PD patients are in support of the hypothesized pathogenetic mechanisms, including mitochondrial dysfunction, oxidative stress, protein degradation involving the lysosomal pathway, inflammatory processes, glial cell activation and cell death. However, sensitive, specific and thoroughly validated diagnostic CSF markers for PD have not yet been identified. Proteins that are related to the pathogenesis and in addition are differently expressed in PD patients compared to controls in affected brain tissue and CSF, such as the antioxidant DJ-1, α-synuclein or the α-synuclein crosslinking protein tissue transglutaminase, may be potential candidate biomarkers. However, the specificity of these candidate biomarkers may be low, due to heterogeneity in disease pathology and pathological overlap with other neurodegenerative disorders. Specificity and sensitivity may be increased by selecting a set of CSF biomarkers and combine them with non-biochemical markers, for example brain imaging or olfactory testing. Unbiased discovery using mass spectrometry based CSF proteomics that includes both PD patients and several other diagnostic groups might yield additional PD-specific biomarkers. Such proteomics findings need to be translated into the development of more convenient multiparameter tests for large-scale analysis and broad application among laboratories. Another important element that is still lacking is the reproduction of findings and large-scale validation of candidate biomarkers, preferentially in neuropathologically confirmed PD patients and in more accessible body fluids such as blood and urine, fluids in which brain tissue proteins may be present in low concentrations. Validation in patient groups of different disease stages as well as longitudinal studies may reveal markers that reflect or predict disease progression. These additional validation steps are essential to enable clinical applicability of CSF biomarkers in PD.

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