Clinically Useful Biomarkers for Parkinson’s Disease

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Editorial

Parkinson’s disease (PD) is the second most common, age-related progressive neurodegenerative disorder after Alzheimer’s disease, primarily affects the elderly, occurring more than 1% of the population over 60 years of age [1,2]. Traditionally, PD has been considered an idiopathic or sporadic disease characterized pathologically by the degeneration and loss of the dopaminergic neurons in the nigral striatal pathway [3]. A recent study reported that PD is more prevalent in Australia and countries of Europe and North America compared with individuals from Asia [4]. Neuropathology is characterized by the inclusions of Lewy bodies and Lewy neurites containing α-synuclein (α-syn) [5,6]. The presence of cytoplasmic α-syn containing inclusions lead to synaptic dysfunction, interfere with axonal transport and thus leads to neuronal damage of vulnerable, neuromelanin rich neurons in the dopaminergic substantia nigra pars compacta’s (SNc) caudal and ventrolateral regions. Neuropathological studies indicate a sequential spreading of the disease process starting in the medulla oblongata, spreading in a cranial direction and eventually affecting the cerebral cortex [7].

PD is a multifactorial disorder where genetic factors, environmental exposures and aging contribute to the risk of developing the disease PD. In both sporadic and genetic PD, the underlying pathophysiological and pathogenetic mechanisms include mitochondrial dysfunction, oxidative stress, Lewy body pathology (α-syn aggregation) and deficits in proteasomal function or autophagy-lysosomal degradation of defective proteins (α-syn) [8,9]. The genetic factors SIPA1L2, INPP5F, MIR4697, GCHH, VPS13C and DDB1K1 are involved in the onset of PD [10]. In a recent meta-analysis studies reported that TNF-1031 polymorphism is a possible risk factor for PD [11]. The roles of the genes parkin, DJ-1, PINK-1 and LRRK2 are not clear in the progression of PD [12]. But Genetic mutations affecting the PINK1 and LRRK2 proteins are related to mitochondrial dysfunction and the formation of reactive oxygen species, which are events involved in PD pathophysiology [13].

Oxidative stress seems to be critical for PD development [14]. In addition to DNA damage [15], lipid peroxidation [16], and mitochondrial dysfunction [17] are other important events in the physiopathology of PD. More specifically, oxidative stress related to the impairment of complex I of the mitochondrial respiratory chain and mitochondrial DNA mutations are essential factors of the PD disease [18]. In this perspective, a group of researchers reported that the use of mitochondrial DNA damage as a biomarker for the susceptibility of dopaminergic neurons in PD [16]. Therefore, the dopamine replacement by using Levodopa has been widely used for three decades in the treatment of PD [19]. After several years of treatment with L-DOPA and related drugs, the majority of PD patients develop L-DOPA-induced-dyskinesia (LID), which is a serious, irreversible adverse reaction to chronic treatment in more advanced stages of PD [20].

The diagnosis of PD usually is clinical and an autopsy is considered necessary for disease confirmation. Unfortunately, the cardinal and defining motor symptoms used in the clinical diagnosis of PD. Early in the disease the diagnostic error rate is about 25% among practitioners with limited clinical experience in PD. This high level of misdiagnosis affirms the strong need for a diagnostic biomarker of PD. Although much progress has been made in PD biomarker research, but clinically useful biochemical markers remain to be identified and validated for early and more precise diagnosis of PD. Presently no available biomarker can able to predict the onset of PD or constitutes a definite diagnostic test. Misdiagnosis often occurs early in the disease and an autopsy is needed to confirm diagnosis. Several biomarkers of PD have been described in the literature, but only a few, none of which are ideal, have found their way into routine clinical practice.

Cerebrospinal Fluid Biomarkers

1. α-Synuclein (α-syn)- is a 140 amino acid presynaptic protein that is abundant in the human brain and exists mainly in a monomeric form [21]. Oligomeric α-syn species are thought to be neurotoxic and have been implicated in the formation of Lewy bodies and Lewy neurites [22]. α-Syn is mainly found in the intracellular space, but can also been found in CSF and in blood. In CSF, α-syn has in many studies been found to be decreased in PD compared with healthy controls [23]. One longitudinal study has shown that an increased level of α-syn within the PD group is associated with future cognitive decline [24]. In contrast, a study on early, untreated PD patients found lower α-syn to be associated with decreased cognitive performance, in particular in the executive attention domain [25]. Levels of phosphorylated α-syn in CSF have also been investigated. One study found increased levels of α-syn phosphorylated at serine 129 (pS129) in PD compared with controls [26].

2. Tau- The tau protein is abundant in high concentrations in areas with non-myelinated cortical axons and is important in stabilizing microtubule [27]. Its hyperphosphorylated form, P-tau has an important role in synaptic plasticity but is also the basis for the formation of fibrillary tangles that are central in AD pathology [28]. In CSF, tau and P-tau are markers commonly associated with AD and both tau and P-tau increased levels compared with controls were reported [29]. In PD however, studies have shown or slightly decreased levels of a tau as well as P-tau in CSF [30].

3. Amyloid beta (Aβ42) - CSF Aβ42 is a biomarker reflecting amyloid pathology. Aβ42 is like tau and P-tau considered a core biomarker for AD where studies have shown decreased levels of Aβ42 [31]. In PD, studies have shown normal or decreased levels of CSF Aβ42 in PD [32]. Low levels of Aβ42 in non-demented PD patients
have been shown to be associated with future cognitive decline and an increased risk of developing dementia and memory impairment [33].

4. NfL- Neurofilament is an important component of the axonal cytoskeleton. Neurofilament consists of three subunits, neurofilament light (NfL), medium (NfM) and heavy (NfH) [34]. NfL is the most abundant small and the most soluble filaments and is unique to the CNS and can therefore serve as markers for neuroaxonal damage [35]. NfL has been found to be increased in CSF in several diseases and it has been found to be increased in atypical parkinsonian disorders [36-38].

Inflammatory Biomarkers

5. YKL-40, also known as chitinase-3-like-1, is a glycoprotein that is upregulated under inflammatory conditions in both peripheral tissue and the CNS [3]. Various studies have been performed on parkinsonian syndromes showing normal or decreased levels in PD but increased in APD [39].

6. IL-6 is involved in the acute phase response. A couple of studies have shown increased levels of IL-6 in de novo PD patients [40]. One study, IL-6 has been shown to be increased in PD patients with cognitive impairment [41].

Genetic Biomarkers

Approximately 10 percent of cases of PD are genetic. Idiopathic PD now is considered to have a complex etiology involving multiple influences including lifestyle, genetics, and environment. Investigations involving associations between single nucleotide polymorphisms in many candidate genes like CYPs, LRRK2, SNCA and parkin [42]. Mitochondrial dysfunction and mutations in mitochondrial genes SNCA and gene products are characterized the underlying cause(s) of the pathology in PD [43]. Many of the gene products of the mutated genes in the autosomal dominant forms have been linked to oxidative stress, mitochondrial dysfunction and mishandling of impaired or aberrant forms of the gene products α-synuclein [44].

Metabolites as Biomarkers

Small molecules/metabolites such as catecholamines, serotonin, aminoacids like glycine, glutamate phenylalanine, tyrosine, tryptophan are also sensitive biomarkers for PD. Other small molecules of interest are glutathione and purine metabolites, including uric acid, because of their role as antioxidants [45,46].

Conclusion

Analytical studies are being carried out in Neuroscience, in particular Parkinson’s throughout the world. The number of people affected with PD will continue to increase as people live to older ages. It is predicted that the progression of PD over 65 years of age will increase from 11.2% in 2002 to 27.6% in 2050. The diagnostic error rate is also high as 25% among practitioners. This high level of misdiagnosis affirms the strong need for a diagnostic biomarker and neuroprotective strategies to help prevent, cure or slow down the disease process in PD.

CSF levels of α-syn, tau, P-tau, NfL and YKL-40 but not Aβ42 increase in patients with PD but remain stable in controls. The levels of NfL are highly useful in the preliminary investigation of patients with parkinsonism, even outside highly specialist settings. Furthermore, α-syn correlates with markers of neurodegeneration (tau and NfL) suggesting an association between α-syn and neurodegeneration. Also, low levels of Aβ42 are associated with subsequent memory decline in PD.

References


