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Review Article

Role of neuron specific enolase as a biomarker in Parkinson's disease

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Abstract

Parkinson's disease (PD) is thought to be the most common neurodegenerative disease with movement disorder. The key motor symptoms are rigidity, tremor, akinesis/hypokinesia/bradykinesia, and postural instability. However, in our day-to-day clinical practice we tend to see several other symptoms which may be motor or non-motor. Non-motor symptoms (NMS) are quite common and debilitating. The pathological hallmarks of PD are loss of dopaminergic neurons in the substantia nigra pars compacta (SNPc) and accumulation of unfolded or misfolded alpha-synuclein. Diagnosis of PD is difficult in the pre-motor stage. Late diagnosis renders a substantial loss of dopaminergic neurons in SNPc and spread of disease in other parts of the brain. This may manifest as either full blown symptoms requiring multiple medications or may even lead to life threatening condition due to lack of early diagnostic tools and techniques. Biomarkers are required to diagnose PD at a very early stage when prevention is possible. Hence, we see a lot of interest among researchers involved in finding a biomarker specific to the disease. Biomarkers may be clinical, image based, genetic, and biochemical. Cerebrospinal fluid (CSF) and serum markers which may correlate with disease pathophysiology are of great significance. One such molecule which recently gained a lot of attention is neuron-specific enolase (NSE). The main aim of this paper is to highlight the role of NSE in predicting neurodegeneration and neuroinflammation ultimately reflecting damage of brain cells in PD.

More Information

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Abbreviations: PD: Parkinson's Disease; NMS: Non-Motor Symptoms; SNPc: Substantia Nigra Pars Compacta; CSF: Cerebrospinal Fluid; NSE: Neuron-Specific Enolase; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; FDG-PET: Fluorodeoxyglucose-Positron Emission Tomography; SPECT: Single-Photon Emission Computed Tomography; MIBG: Metaiodobenzylguanidine; NfL: Neurofilament Light; MAPK: Mitogen-Activated Protein Kinases; PI3K: Phosphatidylinositol 3 Kinase; IFN: Interferon; IL: Interleukin; TNF: Tumor Necrosis Factor; NO: Nitric Oxide; mRNA: Messenger Ribonucleic Acid; TBI: Traumatic Brain Injury; AD: Alzheimer's Disease; MSA: Multiple System Atrophy; DLB: Dementia With Lewy Bodies; H-Y: Hoehn and Yahr; UPDRS: Unified Parkinson's Disease Rating Scale; SCLC: Small-Cell Lung Cancer; NSCLC: Non-Small-Cell Lung Carcinoma; GABA: Gamma Aminobutyric Acid

Introduction

Parkinson's disease [PD] is a common progressive neurodegenerative movement disorder [1]. Most important pathological hallmark of PD is loss of dopaminergic neurons in SNPc and presence of Lewy bodies, which contains an abundant amount of α-synuclein [2,3].

Prevalence of PD is estimated to be around 0.3% in the general population, 1.0% in people over 60 years, and 3% in people older than 80 years in industrialized countries [4]. In European countries estimated prevalence ranges from 65 to 12,500, whereas incidence rates range from 5 to 346 per 100,00 person years [5].

Age is considered to be a significant risk factor for PD [6]. However, risk of men in developing PD is 2 times higher than women, but women have faster progression and higher mortality rate in PD [7]. Pesticides and rural living had been linked to PD [8,9]. Beta2 receptors antagonist is linked to PD, whereas beta2 agonist decreases the risk [10,11].

Statins [12,13], cigarette smoking [8], drinking coffee [14,15], and calcium channel blockers [16] have inverse association in PD. Hyperuricemia or gout [17-20], and use of NSAIDS [21-24] have conflicting evidence. Positive family history is considered to be a risk factor for PD [25]. The relative risk in first-degree relatives of PD cases increases by 2-3 folds if compared to controls [26,27]. 5% - 15% of cases are linked to familial form of PD [28-30]. A handful of genes are linked to PD [28,29,31,32].

Diagnosis of PD is mainly clinical. The diagnostic criteria had been recently updated by movement disorder society (MDS) [33]. It consists of variety of motor and non-motor symptoms. Motor symptoms may include gait disturbances

(freezing of gait, festination, obstacle hesitation) postural abnormalities (PISA syndrome and camptocormia), micrographia, hypomimia, and alterations in eye movements or blinking apart from four cardinal symptoms of tremor, rigidity, bradykinesia, and postural instability [34].

NMS comprises of psychiatric symptoms (apathy, depression, anxiety, hallucination, psychosis), hyposmia, cognitive impairment (mild cognitive impairment and dementia), sensory symptoms, dysphagia, sialorrhea, dysarthria, hypophonia, sleep-wake cycle disturbances, gastro intestinal symptoms (delayed/reduced stomach emptying, constipation), genitourinary symptoms (sexual dysfunction, decreased libido, urinary frequency and urgency) and cardiovascular symptoms (post-prandial and postural blood pressure variations, dysrhythmias) [35-37].

In spite of having a strict diagnostic-criteria of PD, there are several diseases or disorders which can mimic PD. These disorders may comprise of secondary parkinsonism, atypical parkinsonism, and other neurodegenerative diseases [38]. MRI imaging can aid in differential diagnosis, however non-diagnostic for PD per se [39]. Complex imaging like FDG-PET [40], SPECT [41], and MIBG scintigraphy [42,43] can aid in diagnosis of PD. However, the only issue is their availability in small centers and developing world.

Glial cells are known to produce toxic or trophic factors responsible for neuronal cell death or survival [44,45]. Glial cells may be responsible for pathophysiology of neuronal degeneration in PD [46,47]. Few studies have shown that when 50-70% of dopaminergic neurons are lost in SNPc, clinical symptoms of PD manifests [48-50]. Loss of dopaminergic neurons and significant glial reaction are seen in post mortem parkinsonian brains [51]. However, an interesting thing to note is that some neurons are vulnerable to this pathologic process compared to others. It is also reported that dopaminergic neurons easily degenerate in regions with less astrocytes [52-56].

Great interest is seen among research community to find a biomarker for PD which can differentiate PD patients from healthy controls. Until now, only CSF alpha-synuclein and neurofilament light (NfL) chains are considered to be specific for PD. Recently, few researches have focused on NSE and their quantification either in CSF or serum of neurodegenerative diseases [57-59].

Neuron specific enolase and PD

A glycolytic enzyme which catalyzes the conversion of 2-phosphoglycerate (2-PG) to phosphoenolpyruvate (PEP) is enolase. Enolase is known to exist in the form of several tissue-specific isoenzymes, consisting of hetero or homodimers of 3 different monomer-isoforms (alpha, beta, and gamma) [60,61].

NSE also known as human enolase 2 (ENO2) is a 78 kDa gamma-homodimer [62,63]. The NSE gene is located on chromosome 12. It consists of 11 coding exons and spans more than 9213 nucleotides [64]. The biological half-life (t1/2) of NSE in body fluids is approximately 24 hours [62].

It is the dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues [62]. Its levels in other tissues are negligible, except lymphocyte, platelets, and erythrocytes [65]. However, glial cells and astrocytes are also shown to express both homo and heterodimeric forms of the enzyme [60]. γ-enolase is also known to be in cells of the amine precursor uptake and decarboxylation lineage [63,64,66].

NSE is mainly cytosolic but membrane localization is also being reported based on the extracellular milieu and neurotrophicity [62,66]. In a normal state, NSE is not secreted by neuronal cells but only when damage occurs, it is secreted into the extracellular space [62,64,67]. A recent study had found a dual role of NSE, which may be protective or destructive in nature [68]. NSE is known to cause neuroinflammation, neurodegeneration, and even neuroprotection [64,68].

The neurotrophic factor exhibited by NSE is based on two important pathways, MAPK and PI3K which helps in the translocation of enolase to plasma membrane of the cell [63,64,68]. NSE can promote neuroinflammation by activating microglial cells [64,68]. Translocation of enolase to plasma membrane has its downside too because it leads to production and release of proinflammatory cytokines like IFN-γ, IL-1β, TNF-α, NO, chemokines, and reactive oxygen species (ROS) [62,68,69].

NSE is considered as a marker of neurodegeneration as alteration of level is linked to neuronal damage and loss [64,68]. Serum levels of NSE correlated with intracranial bleeding post traumatic brain injury [70,71]. NSE mRNA expression levels have been found to be reduced in postmortem cortical brain tissue in cases with PD [68].

NSE levels in serum and CSF are related to extent of neuronal damage in conditions like ischemic stroke [72-76], TBI [70,71,77], AD [78,79], and MSA [80]. A study by Schaf, et al. did not find any changes in serum levels of NSE in PD patients compared to controls [81].

A recent study by Katayama et al. looked at the CSF NSE of 78 patients which included 27 patients with PD/DLB, 34 patients with non-PD/DLB (other neurodegenerative disorders), and 17 controls. They found out CSF levels of NSE can be used to discriminate PD/DLB from non-PD/DLB because significantly elevated CSF NSE was detected in the non-PD/DLB group [82].

A recent case-control study from Poland looked at CSF NSE levels in 58 PD patients and in 28 healthy control subjects. They found out CSF NSE was significantly increased in PD patients compared to healthy controls. However, no significant correlation was found between CSF NSE levels and

disease severity assessed either in H-Y scale or in UPDRS part III or duration. This shows CSF NSE is not a useful marker to detect progression of the disease.

The authors believe CSF NSE can be promising biomarker of the axonal and glial degeneration seen in PD patients. CSF NSE levels also provided a high discrimination value between PD and healthy controls, with 78.6% sensitivity and 74.1% specificity [83].

Discussion

Enolase is superabundant in cytosol and is a multifunctional enzymatic protein. It has can travel to the plasma membrane on receiving excitatory signals. Membrane expression of enolase is often seen on activated microglia, macrophages, and astrocytes. This can trigger inflammatory response with production of cytokines and chemokines and degradation of extracellular matrix. This may lead to migration of inflammatory cells to the injury site and promote more inflammation. It can behave as a plasminogen receptor and cause damage to tissues when translocated to cell surface [62].

NSE is a cell specific isoenzyme of enolase, which is involved in glycolysis. Expression of NSE in cytoplasm of neurons, which occurs αγ- and γγ-dimer happens late in neural differentiation. It is therefore considered to be a marker for neural maturation over time.

Human NSE is a major brain protein that constitutes between 0.4% and 2.2% of the total soluble protein of brain, depending on the region. In some neurons NSE accounts for 3% - 4% of the total soluble protein [84]. It is specific for peripheral neuroendocrine cells and neurons.

Blood NSE is currently considered as a reliable tumor marker of SCLC as far as diagnosis, prognosis, and follow up is concerned [85,86]. Increased NSE is also reported in NSCLC [87,88]. NSE is also useful at diagnosis of NETs (neuroendocrine tumors) and gastroenteropancreatic (GEP)-NETs [89,90].

Blood levels of NSE is increased in all stages of neuroblastoma, and greater increase has been linked to metastatic disease [91]. It is also increased in malignant pheochromocytoma [92,93], Guillain-Barré syndrome [94], Creutzfeldt-Jakob disease [95-97], carcinoid tumors [98], dysgerminomas [99,100], immature teratomas [101,102], Merkel cell tumor [103], melanoma [104], seminoma [105], renal cell carcinoma [106].

Among neurological diseases, increased NSE is associated with intracerebral hemorrhage [70,71], ischemic stroke [72-76], seizures [107,108], TBI [70,71,77], and comatose patients after cardiopulmonary resuscitation for cardiac arrest [109-113], newborns with perinatal hypoxic-ischemic encephalopathy [114-116], acute spinal cord injury [62,117-119].

It is very evident that serum NSE is studied very less in PD patients and other neurological diseases mentioned above. We need a specific biomarker to diagnosis PD because of the presence of atypical parkinsonism or secondary parkinsonism which can behave the same way as PD in the very early stage when only 10-20% of dopaminergic neurons are lost in SNPc.

Current markers we have now are either not available worldwide or not cost-effective. It is of utmost importance at this juncture to look for blood or CSF biomarker to confirm the diagnosis of PD at an early stage when prevention might be possible along with prognostication, predictability of individual treatment response, and monitoring of disease progression.

PD is associated with cognitive dysfunction. Two known subtypes are mild cognitive impairment and Parkinson's disease dementia (PDD) [120]. The anatomical changes may be seen in several brain parts in PD patients with impairment in cognition. These changes might be seen in a) cerebellum; b) basal ganglia; c) limbic system; d) thalamus; e) hypothalamus; f) glial cells; g) locus coeruleus [121].

Mixed pathology and several underlying pathogenic processes are responsible for uncertainty and underdiagnosis of PD patients [122]. On one hand we have the Braak staging which consists of stage 1-6, where stage 1 being the starting of the spread and deposition of a-synuclein in the lower brainstem and the olfactory system, whereas stage 6 is the neocortical invasion of motor and sensory areas in brain [123-125]. On the other hand, we have an emerging role of striatal neurotransmitters in the pathophysiology in PD. The related abnormalities include, decrease in dopamine, GABA, adenosine and increase in glutamate and acetylcholine [126].

A few scientific papers had also reported the similarity of pathological process in brain of AD and PDD. About 40%-50% of PDD patients may satisfy AD diagnostic criteria [127,128]. Several pathological processes in different stages of disease may be the reason behind absence of a single biomarker specific to PD.

Conclusion

PD is a common neurodegenerative disease where symptoms appear late. It can be divided into prodromal, preclinical, and clinical. Till date, we don't have a single specific and sensitive biomarker to diagnose PD in preclinical stage. About 60% of dopaminergic neurons are already lost in SNPc when clinical symptoms become evident in PD individuals. Specific and sensitive biomarkers are needed to diagnose the disease early. These new biomarkers can be a game changer in diagnosis, identifying individual at-risk of PD, prognosis, individualized therapeutic response, and progression. Researchers should work meticulously in this field with a larger group of PD subjects, in different geographical locations, and in different disease stages to find a single brain derived protein, which will be able to differentiate PD from healthy subjects.

Disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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