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BIOCHEMICAL MARKERS IN PARKINSON'S DISEASE

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Abstrac: Parkinson's disease (PD) is adifficult health problem. Aging may be the onecause of PDfor which the underlyingmolecular mechanism has notbee n clearly identified.Nevertheless, oxidative stressand mitochondrial damage,combine d with adversegenetic and environmental factors, appear to be the major cause of death of dopaminergic neurons in thesubstantia nigra parscompacta.New knowledge On pathogenesis. While there isan increasing influx of patients and the development of new diagnostic modalitiesfor PD, diagnosis still reliesprimarily on physicalexamin ation and clinicaldiagnostic criteria, with a highrate of misdiagnosis. isfurther compli cated by variability in , objective and unbiasedmonitoring of diseaseprogression. PD is often diagnosed at an advancedstage, and neuroprotective therapy is not possible when large numbers of dopaminergic neurons are lost. Given the difficulty of clinical diagnosis of Parkinson's disease, there is an urgent need to identify reliable diagnostic bio-Hermarkers. Intensively tested biomarker candidates includeα-synuclein, DJ-1, 8-hydroxy-2'-deoxyguanosine, 8-hydroxyguanosine,glutathione S-transferase Piprotein for oxidative damage,and inflammatory biomarkers. homocysteine containing C reactive proteinas Currently, none of them are sufficiently specific ands elective. Biomarkers with potentially great specificity,selectivity, and accessibility are miRNAs that enableaccurate and non-

nvasivediagnosticsi. More basicresearch is needed to provide critical data for identifyingthe true cause of Parkinson's disease. Appropriate clinical biomarkers need to bedeveloped in parallel with the collection of data on the occurrence of PD.

Keywords: Parkinson’s disease, biomarkers, α-synuclein, microRNAs, orexin

INTRADUCTION

Parkinson's disease (PD) is a chronic neurodegenerative disease that affects the motor skills of more than 6 million people worldwide. It is the second most common progressive disease after Alzheimer's dementia (AD).The incidence of PD is associated with age (increaseswith age), gender (males are more susceptible to The disease than females), and race (whites are diagnosed more often than AfricanAmericans and Hispanics).The symptoms of Parkinson's disease can be divided into motor and non-motor groups.The motor symptoms of Parkinson's disease vary according to the stage of the disease and typically appear after 80% ofneurodegeneration. They include bradykinesia (slowinitiation of movement),tremor, inability to pass overthe o bstacles, problems with balance, and forward-leaninggait. Non-motor symptoms associated with the PD aredementia, mood swings,hypersexuality, depression,apathy, anxiety, impulsiveness,and others.Recently it was suggested that loss of olfactory ability is associated with onset of the PD and olfactory tests can bepotentially used as earlysensitive clinical marker . The PD is mostly idiopathicdisease, yet 15% of the affected patients have member of their family witht he PD. The PD has fourstages: (i) premotor PD stage(olfactory impairment,cognitive and mood problems,slower bowl movement); (ii)early PD (rigidity, restlessness,trem or, and bradykinesia); (iii)moderate PD (motorsymptoms increase,constipation, and mooddisorders); and (iv) advancedPD (motor and non-

motorproblems worsen, occurrenceof gait, and dementia) .Epidemiological risk factor sfor the PD are: age (the mostprominent), environmentalfactors such as exposure tope sticide rotenone andherbicide Agent Orange,heroin use (via MPTP that is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), and genetics . Surprisingly enough,smoking (nicotine) and consumption of coffee(caffeine) showed protectiveroles against the PD,

However risk factors for other chronic conditions overweight the benefits of smoking associated with the PD . Much healthier protectants are bioactive compounds (e.g. polyphenolquercetin) from foods that canact as antidote for some of abovementioned risk factors(e.g. for rotenone) innormal/damaged neurons .

Epigallocatechin-3-gallate

f ound in green tea prevents conformational changes in α-synuclein associated with formation of Lewy bodies (LB).As explained below, the LB are one of the potential culpritsfor the neurodegeneration in .Berry fruits and their

products are good sources of various polyphenolics hat have protective roles on mitochondrial function greatly involved with etiology of the PD.

Biochemical Biomarkers of Parkinson's Disease

A biomarker is a"characteristic that is objectively measured and evaluated as an indicator of normal biological processes,pathogenic processes orpharmacological responses to a therapeutic intervention "Therefore, an ideal PD biomarker must: (i)differentiate amongst all subtypes of the PD in the premotor stages; (ii) followchanges with the all diseasestages; (iii) be useful formonit oring the effects of novel therapies; (iv)differentiate PD from other neurodegenerative diseases(e.g. progressive supranuclearpalsy (PSP), multiple

systematrophy (MSA), corticobasaldegeneration (CBD), essentialtremor (ER),

etc.); (v) bereproducible, and (vi) beinexpensive and non-invasive .For instance, early differentiation among PD and MSA symptoms has important therapeutic repercussions(both clinical and prognostic),and assessment may be confounded if it is based only on clinical examination .Besides the MSA, diagnosis of PD in early stages may be confounded by other medical conditions with overlapping symptoms (e.g. ER and PSP).

Biomarkers are typical for particular condition and they can be used as indicators of biological processes relevant to some diseases. Further,they should have a positive predictive value which provides risk assessment that patient with a positive result has the disease . Naturally,true positive predictive value of a biomarker should be increased by increasing its sensitivity (probability that patients has biomarker and disease) and by increasing specificity (probability that patients does not have biomarker and disease) .

The PD has poor clinicopathological correlation,meaning it is difficult to predict clinical phenotype just by knowing the pathology, and vice versa. In other words,levels of biomarkers capable of detecting PD pathology may not correlate with relevant clinical data .Example of a good biomarkeris C-reactive protein used for prediction of coronary artery disease, as its levels rise(positively correlate) with increased chances for getting this disease, and drop with application of the successful medical treatment. Currentlys such specific PD biomarker(s)are not yet known, nor the best method for their identification .

Existing biomarkers for the PD can be divided in clinicalbiomarkers (correspond tonon-motor symptoms),neuroimaging biomarkers (e.g.SPECT- single-photonemission computedtomography; PET- positronemission tomography; andfMRI

-functional magneticresonance imaging), and biochemical biomarkers (that are in focus of this review).The clinical biomarkers canserve as additionalconfirmation of the specific and sensitive premotor biomarkers, but sole use indiagnostics is not sensitiveand specific enough .Neuroimaging markers are expensive and inaccessible besides, imaging can detect neurodegeneration only with full development of PD symptoms. Biochemical markers (especially bloodbased and saliva) are the most promising option with minimalinvasiveness and costs. With regards to their objectives,there are two main groups ofthe PD markers, those able to:(i) differentiate predisposedindividuals from healthypopulation prior development of the PD symptoms, and (ii)identify PD with establishedsymptoms

Biomarkers of MitochondrialDysfunction and OxidativeStress

There is a strong connectionbetween oxidative stress,mitochondrial dysfunctionand etiology of the PD The PD has many known sources of ROS and mechanisms for their production including dopamine metabolism,mitochondrial dysfunction,iron, neuroinflammatory cells,calcium, and aging. It isbelieved that alterations inoxidative stress contribute to development of the PD Also,brain of patients affected withthe PD showed increasedlevels of DNA, lipids andprotein oxidation markers .

Biomarkers of AberrantProtein Aggregation and Degradation

α-synuclein

The CSF, blood,gastrointestinal tract and salivary glands are potential matrices for measuring levelsof skin neuro protein .Intensive efforts to study α-synuclein in CSF as adiagnostic PD biomarker have been underway with some promise . However, the assessment yielded conflicting results. One group of results reported that α-synuclein levels decreased in PD patients compared to controls, while the other reported no difference between these groups.

The concentrations of oligomeric types of α-synuclein, total α-synucleinand α-synuclein were measured in plasma to develop blood-based on biomarkers. The result sindicated that plasma levels of phosphorylated α-synuclein. could potentially be used to diagnose PD. In addition, totallevels of α-synuclein can beused as a surrogate marker for the development of PD.This is supported by reports of a positive correlation between plasma levels of unphosphorylated α-synuclein and the progressionof Parkinson's disease.Regardless of the physiological background, the above results imply that the diagnosis "total α-synuclein"or "unphosphorylated α-synuclein" can be used as asurrogate marker for progression of Parkinson'sdisease. Similarly, α-synucleinlevels could be used inpotential clinical trials to test drugs that target α-synucleinpathology and theprogression of Parkinson'sdisease. However, hemolysisaffects the accuracy of determination of levels of α-synuclein in cerebrospinalfluid or in plasma. To this end,Wang et al. others examined the α-synuclein oligomer inerythrocytes by an enzymeimmunoassay. In their study, they showed that the ratio of total α-synuclein protein in erythrocytes was higher in PD patients than in controls,while no significant differencein total α-synuclein proteinwas found between PD and MSA.

Genomics, Proteomics and Metabolomics

Genomics is an important research are a for the development of PD biomarkers. As a result of genetic analysis, numerous mutations associated with the familial or sporadic form of PD have been identified.The main targets for genetic profiling are the genesmentioned above that are associated with the pathophysiology of PD.

mass spectrometry is one of the approaches used in proteomics to detect abnormal proteins resulting from genetic mutations in PD.Such methods have made it possible to identify bio

activeneuropeptides that activatethe G-coupled receptor in the mouse brain. Additional data are required to use this method for diagnostic purposes. Metabolomics is recent discipline that observes influence of the proteins on the production of metabolitesin cellular systems.Metabolites can be excellent source of potential biomarkers that are able to monitor entire course of the disease (including the on setand influence of therapy).Another advantage is that metabolic biomarkers are readily accessible from the CSF, saliva, skin, serum andurine .

Conclusions

In conclusion, PD is serious public health problem that willc ontinue to burden human lives and medical health care systems . Currently, aging is the only probable cause of the PD without clearly identified underlying molecular mechanisms . Nevertheless, it is believed that oxidative stress and mitochondrial damage favored by the detrimental genetic and environmental factors are the main origins of death in dopaminergic neurons from SNc . Hence, fundamentalr esearch (epidemiologic,genetic, animal, etc.) is need to provide this critical data in order to determine real reasons behind the PD.Parallel to obtaining data for the origins of the PD,development of the suitable clinical biomarkers should follow. Although there are plenty of new data on pathogenesis, pathoanatomy,and development of new diagnostic for the PD (SPECT,PET, fMRI), still diagnosis ofthe PD heavily depends on degeneration of the SN cells and the physical examination and clinical diagnostic criteria.Unfortunately misdiagnoserate is fairly high (10-50%)even by movement disorderspecialist .This is furthercomplicated as PD symptoms tend to fluctuate with time and hinder objective and unbiased monitoring of disease progression This disease is often diagnosed when degenerative process is in the advanced stage and when more than 80% of dopaminergic neurons of the SN are lost .In that stage apotential neuroprotective therapies are not possible,only symptomatic ones. Givent he difficulties with clinical

diagnosis of the PD(particularly in earlier stagesof the disease when neuropretection is possible),there is a pressing need to identify reliant diagnostic biomarkers.

The development of biomarkers that will predict,diagnose, evaluate, and prognosticate PD is essentialfor patient's health care and research . In addition,unbiased discovery is underway using techniques including metabolomics,proteomics, and transcriptomics (geneprofiling) . Recently, it was also suggested that post-transcriptional regulation has important role in molecular mechanisms for PD. Several potential biomarkers identified in other diseases or in other types of biological fluids are investigated as blood-based biomarkers for the PD.

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