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Towards a biomarker system that supports disease modifying therapies in Parkinson's disease

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A biomarker system to evaluate investigational disease-modifying drug effects in Parkinson's disease (PD) remains largely unavailable. In Alzheimer's disease (AD), investigation of novel drug candidates may rely on the A/T/N system that may collectively represent possible pathological changes in the AD brain.[1] PD research is lagging behind other neurodegenerative diseases, like AD, because of a less urgent need to find new drugs owing to the availability of effective dopaminergic medications and other symptomatic therapies. The market of PD drugs is substantial and includes dopamine replacement therapies (levodopa), monoamine oxidase inhibitors to reduce dopamine catabolism, dopamine agonists, and amantadine. Many of these drugs have been formulated to include immediate- versus extended-release formulas as well as different routes of delivery (eg, sublingual, nasal, pumps, patches, oral). Deep brain stimulation is a surgical option to treat some PD symptoms, which include approximately 20 motor, cognitive, behavioral, and autonomic symptoms. However, PD remains a progressive, multi-symptom disease that requires increasingly more medications

as the disease worsens. There is a great unmet need to develop disease modifying therapies that not only individually manage the multiple symptoms of PD but collectively modify possible pathologies. This includes dopaminergic medications and therapies to reduce abnormal protein aggregation. Abnormal proteins in PD include oligomeric alpha-synuclein and hyperphosphorylated tau. The normal functioning of these proteins is integral to the brain's motor system. Measurement of these potential biomarkers together as a "kit" may help with evaluating the efficacy of disease modifying drugs.

The motor system in Parkinsonism

PD is the second most common neurodegenerative disorder causing motor and non-motor symptoms, loss of dopaminergic neurons in the nigrostriatal system, and accumulation of misfolded alpha-synuclein.[2-4] The diagnostic error at the onset of motor symptoms is often significant, and PD may be confused with other alpha-synucleinopathies, such as dementia with Lewy bodies (DLB) or multiple system atrophy (MSA), due to the presence of misfolded alpha-synuclein in Lewy bodies (LBs) seen in the autopsies of PD patients. The overlap in motor symptoms between PD and the primary tauopathies, including progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), is high. Atypical parkinsonian syndromes (APS), including PSP, CBD, and MSA, may be difficult to distinguish in early stages and are often misdiagnosed as PD. Drug challenge with dopamine or a DaTscan, a radiopharmaceutical indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT), may assist in the evaluation of patients with suspected Parkinsonian syndromes (PS). However, the classification of motor symptoms into specific diseases remains very challenging, and it may take time for the disease to progress and the symptoms to become clearer to help narrow the differential diagnosis. Therefore, investigating potential disease modifying drugs in early stages of the disease depends on the ability to measure biomarkers that are likely to change in response to drug candidates.

Alpha-synuclein

Alpha-synuclein gene (SYN) duplication, multiplication, and mutations were identified as causal genetic factors in familial PD. In idiopathic PD,[5] misfolded alpha-synuclein accumulates in LBs. These findings indicate that misfolding of alpha-synuclein is a critical pathology in PD. In post-mortem studies, LBs are found throughout the brain, including the surviving dopaminergic neurons in the nigrostriatal system and the cortex.[2] The cerebrospinal fluid (CSF) levels of alpha-synuclein oligomers increase in PD while total alpha-synuclein decreases compared to aged-matched controls.[6-8] These data indicate that an important distinction must be made between normal, natively unfolded alpha-synuclein, that are referred to as "total levels" and have an essential housekeeping function, and the misfolded oligomers, that may form toxic fibrils and induce LB pathology. The toxicity of alpha-synuclein is due to the transitional oligomers that are the building blocks of fibrils.[9] These transitional oligomers are measureable in the CSF of idiopathic PD, and they seem to change in response to disease-modifying drug candidates compared to total levels of alpha-synuclein which remain stable.[10] In animal models, accumulation of alpha-synuclein aggregates impairs dopamine transmission, but elimination of these aggregates enhances dopamine release and utilization in the nigrostriatum.[11] A reduction of alpha-synuclein oligomers results in improved dopaminergic neuronal activity in PD patients.[10] Therefore, the concurrent measurement of oligomeric alpha-synuclein and dopamine may provide an index of functional activity of the dopamine neurons. Total and oligomeric alpha-synuclein, as well as dopamine metabolites homovanillic acid (HVA) and 3,4-Dihydroxyphenylacetic acid (DOPAC), are reliably measured in the CSF of PD patients.[10] The brain may contribute 10-15% of the circulating plasma levels of HVA.[12] Most circulating HVA is due to intestinal metabolism of dopamine while DOPAC is a principal metabolite of brain dopamine and is transported from the brain to the plasma for excretion.[13] Therefore, both CSF and plasma levels of dopamine metabolites give an indication of dopamine utilization and metabolism in the brain.

Tau

Early signs and symptoms of PD may include tremor, slowed movement (bradykinesia), rigid muscles, impaired posture and balance, loss of automatic

movement, speech difficulties, and writing changes. PD is highly heterogeneous and may present several phenotypes that are characterized as tremor-dominant (TD) or postural instability/gait difficulty (PIGD) subtype.[14] Midbrain (or mesencephalon) structures, including the tectum, tegmentum, substantia nigra, crus cerebri, and cranial nerve III and IV nuclei (oculomotor and trochlear), are the fundamental centers of locomotion, gait, and speed.[15,16] The pontocerebellum (which receives inputs from the cerebral cortex via the pontine nuclei), the spinocerebellum (which receives afferents from the spinal cord), and the vestibulocerebellum dominate motor control and balance.[17] Highly complex neuroanatomy is involved in posture-gait control via somatosensory (visual and vestibular) information, postural reflexes, and reticulospinal pathways (arising from the lateral part of the mesopontine tegmentum and spinal cord) as well as cognitive information at the temporoparietal association cortex, motor cortical areas, basal ganglia, and cerebellum. Consequently, impairments in cognitive function resulting from damage to the cerebral cortex, basal ganglia, and cerebellum may disturb posture-gait control.[18] At the macroscopic level, loss of substantia nigra is seen in PD, MSA, and PSP which correlates with parkinsonism. These distinguishing macroscopic features in the three major degenerative parkinsonian disorders are also the basis of neuroimaging biomarkers in the living patient.[19] For example, in MSA there is atrophy of the pontine base, whereas the pontine base is unremarkable in PD and PSP. There is atrophy of the cerebrum at the level of the subthalamic nucleus (STN) in PSP, whereas the STN is normal in PD and MSA. In MSA, there is atrophy of the posterior putamen, but no atrophy is present in PD or PSP. Hyperphosphorylated tau and alpha-synuclein pathologies coexist in PD and other parkinsonian disorders that share considerable overlap of their clinical signs and symptoms.[20] While extrapyramidal signs in PD seem to be linked to nigrostriatal dopaminergic impairment, non-motor and autonomic dysfunction (cardiac and gastrointestinal), hyposmia, depression, rapid eye movement (REM) disturbances, behavioral disorders and, dementia may antedate motor dysfunction and are linked to other brainstem and cortical brain areas.[21] Tau expression in various PS in the midbrain and other motor tracts indicate that the emphasis of any disease modifying therapy should include the whole brain's motor system. [22-24]Gross neuropathological examination reveals brain atrophy, especially in the frontal and temporal lobes, and selective atrophy of the basal ganglia and brainstem nuclei in the primary tauopathies associated with dementia

and parkinsonism. Frontotemporal dementia (FTD) and parkinsonism linked to chromosome 17 (FTDP-17) are autosomal dominant neurodegenerative disorders caused by mutations in the tau gene that exhibit three clinical features: behavioral and personality changes, cognitive impairment, and motor symptoms. The major microscopic feature of FTDP-17 is the presence of neuronal and glial neurofibrillary tangles composed of insoluble tau protein.[25] PSP is characterized pathologically by four-repeat (4R) tau deposition in various cell types and anatomical regions, mainly the brainstem and midbrain.[26] Therefore, hyperphosphorylation of tau in primary tauopathies leads to motor and non-motor symptoms that overlap with PD, and it should be considered an integral part of a PD biomarker mix that can represent the regional and molecular basis of motor and non-motor symptoms in PD and other PS. Similar to oligomeric alpha-synuclein, hyperphosphorylated tau is present and detectable in the CSF of PD patients.[10]

Conclusion

To investigate disease-modifying drug candidates in PD, clinical outcomes should be measured with a biomarker system that includes CSF and plasma levels of dopamine metabolites in addition to assessment of CSF oligomeric alpha-synuclein and hyperphosphorylated tau. This system is likely to represent the pathology in the motor system and may collectively represent biomarkers associated with motor and non-motor symptoms in PD.

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Disclaimer

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