Biomarkers of Parkinson Disease and Related Disorders

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Country

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Biomarkers of Parkinson Disease and Related Disorders

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Parkinson's disease & PD-related disorders|Alzheimer's disease & other dementias

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Research Abstract

(1) In autonomic synucleinopathies, neuroimaging biomarkers predict survival: About 1/3 of Parkinson disease (PD) patients, most multiple system atrophy (MSA) patients, and all pure

autonomic failure (PAF) patients have neurogenic orthostatic hypotension (OH). In a prospective cohort study we compared long-term survival in these synucleinopathies. We found that survival depends on the particular disease, with the time to death shorter in MSA than in PD+OH and in PD+OH than in PD without OH or in PAF. Importantly, the analysis also demonstrated differential survivals based on results of 18F-DOPA putamen and 18F-dopamine (18F-DA) cardiac neuroimaging, regardless of the clinical diagnosis (Goldstein DS, Holmes C, Sharabi Y, Wu T. Long-term survival in synucleinopathies: A prospective cohort study of Parkinson disease, multiple system atrophy, and pure autonomic failure. Neurology 2015;85;1554-1561). (2) A pattern of cerebrospinal fluid (CSF) catechols provides a specific biomarker of parkinsonism: We published previously that PD and MSA involve decreased CSF levels of 3,4-dihydroxyphenylacetic acid (DOPAC). One might expect this, since DOPAC is the main neuronal metabolite of dopamine (DA). In the cytoplasm dopamine undergoes enzymatic oxidation to form DOPAC and spontaneous oxidation to form 5-S-cysteinyl-dopamine (Cys-DA). Our laboratorys unique capability to assay DOPAC and Cys-DA simultaneously led to the discovery that in PD and parkinsonian MSA (MSA-P), CSF Cys-DA/DOPAC ratios averaged more than twice control, whereas in PAF the mean Cys-DA/DOPAC ratio was normal. Therefore, in synucleinopathies an elevated CSF Cys-DA/DOPAC ratio seems to provide a specific biomarker of parkinsonism. Oxidative stress or decreased activity of aldehyde dehydrogenase (ALDH) in the residual nigrostriatal dopaminergic neurons may explain the increased CSF Cys-DA/DOPAC ratios in parkinsonian synucleinopathies. (Goldstein DS, Holmes C, Sullivan P, Jinsmaa Y, Kopin IJ, Sharabi Y. Elevated cerebrospinal fluid ratios of cysteinyl-dopamine/3,4-dihydroxyphenylacetic acid in parkinsonian synucleinopathies. Park Rel Dis 10.1016/j.parkreldis.2016.07.009. (PMID 27474472). (3) Biomarkers of deficient vesicular storage are associated with catecholaminergic neurodegeneration in autonomic synucleinopathies: We retrospectively analyzed data from 20 conditions with decreased or intact catecholaminergic innervation, involving different etiologies, pathogenetic mechanisms, and lesion locations. All conditions involving parkinsonism had accelerated loss of putamen 18F-DOPA-derived radioactivity; in those with post-mortem data there were also decreased putamen dopamine (DA)/DOPA ratios. All conditions involving cardiac sympathetic denervation had accelerated loss of myocardial 18F-DA-derived radioactivity; in those with post-mortem data there were increased myocardial dihydroxyphenylglycol/norepinephrine (DHPG/NE) ratios. All conditions involving localized loss of catecholaminergic innervation had evidence of decreased vesicular storage specifically in the denervated regions. Thus, across neurodegenerative diseases, loss of catecholaminergic neurons seems to be associated with decreased vesicular storage in the residual neurons. (Goldstein DS, Holmes C, Mash D, Sidransky E, Stefani A, Kopin IJ, Sharabi Y. Deficient vesicular storage: A common theme in catecholaminergic neurodegeneration. Parkinsonism Relat Disord 2015;21:1013-1022.) (4) Immunofluorescence confocal microscopy provides in vivo and post-mortem biomarkers that link sympathetic noradrenergic denervation with intra-neuronal alpha-synucleinopathy: As part of the Autonomic Rare Diseases Clinical Research Consortium (RDCRC) we are supplying to collaborators at Harvard skin biopsy tissues for confocal microscopy of immunofluorescent alpha-synuclein and tyrosine hydroxylase (TH). This approach may provide a visual biomarker of axonal degeneration and alpha-synuclein deposition in sympathetic noradrenergic fibers–a smoking gun linking Lewy body diseases with catecholaminergic denervation. Within our Section we have begun a project on immunofluorescence confocal microscopy in catecholamine-related disorders. Based on this technology, as well as clinical neurochemical and sympathetic neuroimaging techniques, we preliminarily identified a case of autoimmunity-associated

autonomic failure with sympathetic denervation and partial re-innervation. We also have obtained preliminary evidence for intracellular co-localization of immunoreactive alpha-synuclein and TH in sympathetic ganglion and myocardial tissues in Lewy body diseases. (5) Biomarkers of catecholaminergic neurodegeneration predict PD: The intramural NINDS PDRisk study (NIH Clinical Protocol 09-N-0010) is testing whether in individuals with multiple risk factors for PD neuroimaging or neurochemical biomarkers of catecholamine deficiency predict outcome after up to 7.5 years of follow-up (5 visits at 1.5-year intervals). We report the results of data analysis after the first phase (3 follow-up years). In this prospective cohort study, participants entered information about family history of PD, olfactory dysfunction, dream enactment behavior, and orthostatic hypotension at a protocol-specific website. After confirmation of at least 3 risk factors at the NIH Clinical Center, subjects underwent inpatient testing of central and cardiac catecholaminergic innervation, by putamen 18F-DOPA and myocardial 18F-dopamine positron emission tomographic scanning and CSF DOPA and DOPAC levels. Subjects were then followed at about 18-month intervals. The primary endpoint was a diagnosis of PD. We took a first look at the follow-up data after accrual of 30 participants. Of 3,176 individuals providing their risk factor data, 388 had at least 3 risk factors, 31 underwent inpatient biomarkers testing, and 22 were followed for at least 3 years. Four subjects developed PD (POSITIVE group); 18 did not by 3 years (NEGATIVE group). Values for the posterior/anterior ratio of putamen 18F-DOPA-derived radioactivity, CSF DOPA, septal myocardial 18F-dopamine-derived radioactivity, and CSF DOPAC each distinguished the POSITIVE group. Based on dichotomized data, at 3 years the sensitivity and specificity of a low putamen/occipital cortex ratio combined with a low CSF DOPA level were 100%. Thus, in people at risk for PD, biomarkers of catecholamine deficiency seem to predict PD at 3 years of follow-up.

Lay Summary
Further information available at:

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