Metabolism

Personalized medicine strategies for managing patients with Parkinsonism and cognitive deficits

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ABSTRACT

Patients exhibiting the classic manifestations of parkinsonism – tremors, rigidity, postural instability, slowed movements and, sometimes, sleep disturbances and depression – may also display severe cognitive disturbances. All of these particular motoric and behavioral symptoms may arise from Parkinson's disease [PD] per se, but they can also characterize Lewy Body dementia [LBD] or concurrent Parkinson's and Alzheimer's diseases [PD & AD]. Abnormalities of both movement and cognition are also observed in numerous other neurologic diseases, for example Huntington's Disease and the frontotemporal dementia. Distinguishing among these diseases in an individual patient is important in "personalizing" his or her mode of treatment, since an agent that is often highly effective in one of the diagnoses (e.g., L-dopa or muscarinic antagonists in PD) might be ineffective or even damaging in one of the others. That such personalization, based on genetic, biochemical, and imaging-based biomarkers, is feasible is suggested by the numerous genetic abnormalities already discovered in patients with parkinsonism, Alzheimer's disease and Huntington's disease (HD) and by the variety of regional and temporal patterns that these diseases can produce, as shown using imaging techniques.

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1. Introduction

At some point in their clinical histories the majority of patients manifesting parkinsonism also develop significant cognitive impairments involving deficits in visuospatial, attentional, memory, and executive functions, and in many cases these impairments progress to frank dementia [1]. Even at the time the patients are first seen by a neurologist approximately 20% satisfy criteria for MCI (mild cognitive impairment) [2].

At least three disease entities, confirmable histopathologically at post-mortem examination, frequently give rise both to cognitive disturbances and to the classic tremors, rigidity, postural instability, sleep disorders, depression and slowed movement observed in patients with parkinsonism: Parkinson's Disease per se [PD, or PDD for patients also exhibiting dementia]; Lewy Body dementia [LBD]; and concurrent affliction

with both Parkinson's and Alzheimer's Diseases [PD+AD]. Determining which of these diagnoses applies in a particular patient so that his or her treatment can be appropriately personalized is often difficult because of wide variability in symptom presentation. Moreover, it is still debated whether LBD and PDD are actually distinct disease entities or simply different phenotypes of shared disease processes [3]. However, assigning a diagnosis is important: For example, the generic drug levodopa, used effectively for the past four decades as initial therapy in PD, is often poorly effective in patients with DLB [4]. Similarly, while PD is often treated with drugs that block muscarinic cholinergic receptors, patients with the cognitive deficits of AD generally receive cholinesterase inhibitors to enhance central cholinergic transmission. Sometimes the patient's clinical history argues strongly in favor of one of these diagnoses: Thus PDD requires that the motor symptoms

precede the dementia by at least a year, while in LBD most patients display dementia concurrent with or even prior to their initial motor symptoms, and cognitive functions typically fluctuate and decline more rapidly than in PDD [5]. PDD patients tend to exhibit severe tremor, and their motor abnormalities are often asymmetric. LBD patients often describe visual hallucinations and severe sleep disturbances, while those with PDD typically manifest early impairments in face recognition, attention, and planning [6]. AD patients – including those with both PD and AD – usually show greatest impairment on memory testing, while those with PDD or DLB are more limited by visuoperceptual, visuoconstructive, and attentional deficits [7].

No patterns of genetic, radiologic, and biochemical biomarkers have yet been canonized as proving one of these diagnoses, except perhaps the characteristic autosomal dominant mutations of HD. However in AD major progress is being made towards formulating such a panel of biomarkers [8]. It presently includes: low Abeta 1-42 and high tau or phosphorylated tau concentrations in the CSF; volume loss of hippocampus, entorhinal cortex, and amygdala as assessed using imaging technologies; high cortical binding of Florbetapir [9], a PET-visualizable beta-amyloid ligand; and the existence of a proven AD-related autosomal dominant mutation within the patient's immediate family. This panel can, theoretically, be used to distinguish among clinical subsets of AD patients, thus decreasing the numbers of subjects needed to power studies of putative treatments, and facilitating choices of optimal treatments for individuals when such treatments become available, It can be hoped that comparable progress will soon be made for PD and LBD so that "Personalized Medicine" strategies will become canonized for managing patients who exhibit signs of parkinsonism or of parkinsonism plus dementia. One additional marker might turn out to be a patient's ability to exhibit a robust therapeutic response to L-dopa, — present in PD or PD+AD, but usually not in LBD.

PD, DLB, and AD apparently share some common pathogenetic features:

All three are associated with major losses of particular groups of synapses and, ultimately, the presynaptic mostly-dopaminergic neurons that give rise to these synapses;

The losses of synapses are thought to result from the locally-toxic effects of soluble and insoluble polymers of specific presynaptic proteins; mutant forms of those proteins; or fragments of the protein, (e.g. alpha-synuclein, ubiquitin, Pael-2, and synphilin-1 for PD; alpha-synuclein for DLB; beta-amyloid1-42 for AD). A similar mechanism involving a mutant protein, huntingin, is thought to cause the neuronal loss in HD.

The proteins and/or fragments can aggregate to form large, insoluble visible structures (i.e., the round, intracytoplasmic, and eosinophilic Lewy bodies contained within neuronal nuclei, in PD and DLB; amyloid plaques in AD). Such structures had formerly been thought to be neurotoxic, however they are now more commonly viewed as inert or possibly even neuroprotective. Rather, the toxic moiety is thought to be soluble oligomers of alpha-synuclein in PD or DLB [10] or of Abeta1-42 in AD [11,12]. Both Lewy bodies and amyloid plaques are also found in brains of normal elderly people, and Lewy bodies can also be present in peripheral neurons, e.g. in the intestinal myenteric plexus or the cardiac sympathetic plexus.

The presumably-toxic aggregates also damage, in all three diseases, the dendritic spines which are essential precursors of new synapses; hence the net loss of synapses reflects both accelerated synaptic turnover and slowed synaptogenesis. One school of neurologists, following Dr. Heiko Braak, holds that the earliest neuropathologic evidence of PD is usually found in the olfactory bulb and medullary brainstem; the more conventional view is that PD pathology first afflicts the substantia nigra. In any case there is considerable interpatient variety in the neuronal populations involved, and in the abnormal proteins and aggregates within afflicted neurons.

It should be noted that levels of Abeta1-42 in human brain and CSF can be reduced by agents that block its synthesis (gamma-secretase inhibitors) or remove it from the circulation (by causing it to bind to antibodies.) However no study has yet demonstrated that doing so produces clinical improvement in AD patients. No tools are yet available for reducing levels of alpha-synuclein, nor any of the other proteins thought to be aberrant in PD, PDD, DLB or HD.

Numerous mutations, discussed below, of the gene (SNCA) that codes for alpha-synuclein have been associated with the development of PD, DLB, and related neurodegenerative diseases [13], just as those in the gene coding for the amyloid precursor protein (APP) can be associated with the early development of AD. Mutations in at least 16 genes have also been shown to constitute risk factors for PD or to underlie familial forms of Parkinsonism [14]. Some examples include:

1. The glucocerebrokinase gene. Among Ashkenazi Jews, a mutation in this gene (which is also associated with Gaucher's disease) can constitute a risk factor for PD. Patients with this mutation tend to have a younger age of disease onset; a greater likelihood of cognitive impairment; less prominent tremor, rigidity, and bradykinesia; and less asymmetry in their presenting symptoms.
2. The alpha-synuclein gene, usually, when mutated, a risk factor for PD but also sometimes producing autosomal dominant disease. Complexes of the modified alpha-synuclein protein can combine with another protein, ubiquitin, and aggregate to form protofibils and then fibrils in Lewy bodies. (The normal function of the alpha-synuclein molecule is poorly understood.) Such mutations are also associated with a younger age of disease onset; more rapid disease progression; more cognitive impairment and even dementia; and with such CNS symptoms as hallucinations and orthostatic hypotension.
3. The gene for leucine-rich repeat kinase-2 protein. Mutations in this gene are probably the most common monogenic promoter of PD, causing both familial and sporadic disease, usually without cognitive impairment and with asymmetric tremor.

Genetic testing is available for some of these 16 genes or the proteins they generate, however there is no consensus as to how data from such tests should be interpreted, and routine testing for them is not currently recommended [15,16]. Too few data are available on the range of mutations that might be associated with DLB to draw conclusions as to whether its pattern of genetic abnormalities differs from that seen in PD. Inasmuch as the incidence of DLB is discordant

among monozygotic twins; it seems likely that environmental or other epigenetic factors are important contributors to DLB's pathogenesis [17]. Allelic variations among genes for enzymes that metabolize drugs used to treat PD or DLB could also affect the design of a patient's "personalized medicine" strategy: For example, the efficacy of a drug given to enhance levodopa's efficacy by blocking its O-methylation was greater among patients with the high Val/Val catechol-O-Methyltransferase (HH) allele than among those with the low (Met/Met (LL) allele [18].

PD is also heterogeneous with respect to the brain regions affected; the sequence with which damage appears in particular regions; and the sequence with which the resulting motor and behavioral symptoms appear. Characterization of this brain sequence in individual patients, using imaging techniques [19], may assist in formulating their optimal "personalized medicine" strategies, and in differentiating PD from LBD and PD-AD and related diseases like the frontotemporal dementia [20]. Magnetic resonance imaging (MRI) and transcranial sonography techniques can be used to detect disease-induced changes in the structure of the substantia nigra, and diffusion tensor imaging and tractography can examine the integrity of neuronal pathways in the brain [19]. Positron emission tomography (PET) scanning and single photon emission computer tomography (SPECT), using isotopically-labeled tracers, can provide information about the status of the hallmark presynaptic dopaminergic (e.g., nigrostriatal) terminals, as well as about postsynaptic dopamine receptor activity, brain dopamine levels and release, and functional changes in related nondopaminergic brain pathways [19] . It will be of considerable interest to determine whether Parkinsonian patients with particular genetic abnormalities also have characteristic sequences of neuropathologic progression as assessed by imaging techniques.

Major longitudinal studies are underway to characterize the points in their clinical histories when patients develop useful biomarkers for PD [21], with and without dementia.

In conclusion, personalized, properly targeted treatment of patients exhibiting signs of both parkinsonism and cognitive loss depends on personalized diagnosis. Without personalized, and therefore accurate, diagnosis, the treatment selected may prove to be inappropriate, ineffective, and even deleterious.

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