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Diagnosing dementia in extrapyramidal disorders

Dementia, particularly Alzheimer's disease (AD), and parkinsonism, mainly Parkinson's disease (PD), are two of the most common age-related neurodegenerative disorders. The former belongs to the family of tauopathies, the latter is a form of synucleinopathy. Alpha-synuclein (α -syn) and tau polymerize into amyloid fibrils and form intraneuronal filamentous inclusions (Lewy bodies, LBs, and neurofibrillary tangles, NFT, respectively). It has recently been shown that α -syn and tau can promote their fibrillization and drive the formation of pathological inclusions in different neurodegenerative diseases [1].

Although AD and PD have been traditionally considered separate clinical entities, the recognition of extrapyramidal features in up to 30 to 70% of clinically diagnosed AD patients and the increasing number of studies demonstrating the presence of dementia in patients with PD have changed this strict dichotomy.

Key words Parkinson's disease • Parkinson's disease-dementia complex • Dementia with Lewy bodies

Extrapyramidal syndromes with dementia can be classified according to morphological and biochemical features in: *α -synucleinopathies* (Parkinson's disease with and without dementia, Lewy body disease, including dementia with Lewy bodies, and the Lewy body variant of AD, multiple system atrophy, Hallervorden-Spatz Disease), *tauopathies* (progressive supranuclear palsy, corticobasal degeneration, argyrophilic dementia, subcortical progressive gliosis), *polyglutamine diseases* (Huntington disease, coreoacantocytosis, Machado-Joseph disease, dentate-rubro-pallido-luysiane atrophy) and other rare genetic syndromes. In the clinical setting, dementia syndromes most commonly encountered in patients with parkinsonism are Parkinson's disease with dementia (PDD) and dementia with Lewy Body (DLB). Although consensus clinical criteria have been validated for DLB, no formal clinical diagnostic criteria have been proposed or validated for PDD. An arbitrary "1-year rule" has until now been used to separate DLB from PDD: onset of dementia within 12 months of parkinsonism qualifies as DLB, and more than 12 months of parkinsonism before dementia as PDD [2]. Likewise, pathological criteria separating these two disorders are not available yet. It should also be pointed out that autopsy studies on patients with clinically diagnosed DLB and PDD show heterogeneity in terms of distribution and density of LB pathology, AD pathology (i.e., NFT) and vascular pathology [3]. Moreover, the classic LB pathology can commonly be seen outside the clinical spectrum for DLB, which means that factors other than the absolute number of LB in the neocortex and limbic system may influence the development of cognitive impairment in PD [4].

In PDD patients the neuropsychological pattern is characterized by a prominent impairment of executive functions associated with a slowing of thought processes and a relative sparing of memory and other cortical functions. The neuropsychological characterization of

DLB shows a mixed cortico-subcortical pattern. DLB patients exhibit equivalent deficits in many cognitive abilities affected by AD but have disproportionately severe deficits in executive, intentional, and visuospatial processing.

In the course of PD, patients can become cognitively impaired. It has recently been shown that there are significant correlations between the cognitive status of patients and the stage of the PD pathology and between cognitive status and Hoehn and Yahr stages [5, 6].

In PD, the risk of developing dementia increases along with the disease progression in the brain. These results are similar to those achieved in studies examining the relationship between cognitive status and the AD-associated neurofibrillary changes. Since the pathology and the clinically recognizable symptomatology of PD are progressive, the gradually increasing severity of the brain lesions may contribute to a decline of cognitive functions long before symptoms have become severe enough to warrant the diagnosis of dementia. Therefore, a prodromal phase, such as mild cognitive impairment (MCI) in AD [7], presumably precedes overt dementia. Based upon the topographical extent of α -synuclein-immunopositive Lewy neurites and Lewy bodies, staging of PD brain pathology has been recently proposed [5] (Table 1). Current clinical diagnostic criteria are limited exclusively to the assessment of specific somatomotor dysfunctions. This might be due to the fact that PD first comes to the attention of the clinician when the brain lesions correspond to stage 3 or above. The initial decline from intact cognition occurs during stages 3 to 4, or earlier, around the same time as the manifestation of the first somatomotor dysfunctions. Thus, a transitional period of MCI analogous to that described for AD also exists in PD. In the light of diagnosing the prodromal phase of neurodegenerative dementia disorders, namely

AD, nowadays it is generally accepted the usefulness of combining neuropsychological, neuroradiological and biochemical markers, in order to achieve the highest diagnostic accuracy [8]. Neuroradiological data about the medial temporal lobe atrophy (MTA) suggest that patients with PD without dementia had greater MTA on MRI than aged-matched control subjects but less than subjects with DLB and AD. MTA has been seen in cognitively intact older subjects with PD and is not more pronounced in PDD. AD and, to lesser extent, DLB, show more pronounced MTA. Therefore, in PD patients, the two presymptomatic markers for dementia risk might be represented by impairment of executive functions in conjunction with hippocampal atrophy [9]. Cerebrospinal fluid (CSF) biomarkers have shown to reliably predict the conversion of MCI to AD [10]. Thus, it might be of value to have also this information when diagnosing cognitive deterioration in a patient with extrapyramidal disorder. To this purpose, we have first studied the CSF biomarkers (A β 42, total tau and phosphorylated tau) in PD, PDD and DLB. According to our data, PD patients show normal CSF biomarkers, independent of disease duration. DLB is characterized for a lower A β 42 and total tau values higher than PDD. Interestingly, only in PDD the duration of disease is correlated with an increase of both total tau and p-tau.

Preclinical diagnosis of dementia occurring in the course of neurodegenerative diseases, and specifically in extrapyramidal disorders, is a challenge for the diagnostic ability of the clinician. At present we only have symptomatic treatments. However, in view of availability of disease-modifying agents, the preclinical diagnosis will be mandatory and biomarkers will represent the most reliable way to monitor the drug efficacy. Therefore, implementation of clinical research in this field is highly needed.

Table 1 Stages in the evolution of PD-related pathology (modified from [5])

Presymptomatic stages	
Stage 1, medulla oblongata	Lesions in the dorsal IX/X motor nucleus and/or intermediate reticular zone
Stage 2, medulla oblongata and pontine tegmentum	Pathology of stage 1 plus lesions in caudal raphe nuclei, gigantocellular reticular nucleus, and coeruleus-subcoeruleus complex
Symptomatic stages	
Stage 3, midbrain	Pathology of stage 2 plus midbrain lesions, in particular in the pars compacta of the substantia nigra
Stage 4, basal prosencephalon and mesocortex	Pathology of stage 3 plus prosencephalic lesions. Cortical involvement is confined to the temporal mesocortex (transentorhinal region) and allocortex (CA2-plexus). The neocortex is unaffected
Stage 5, neocortex	Pathology of stage 4 plus lesions in high order sensory association areas of the neocortex and prefrontal neocortex
Stage 6, neocortex	Pathology of stage 5 plus lesions in first order sensory association areas of the neocortex and premotor areas, occasionally mild changes in primary sensory areas and the primary motor field

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