

## IS THERE A COGNITIVE DYSFUNCTION IN EARLY PD? YES

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At present, it is broadly recognized that Parkinson's disease (PD) is a complex neurodegenerative disorder with characteristic motor manifestations and a diversity of non-motor symptoms (NMS). Some of these NMS may precede, even for years, the beginning of the motor symptoms (e.g., depression, constipation, REM sleep behavioral disorder), whereas other are more frequently present in advanced phases of the disease (e.g., hallucinations, urinary incontinence, dementia). Epidemiological studies show that severe cognitive impairment fulfilling the criteria for diagnosis of dementia is present in 24-31% of patients with PD (Aarsland et al. *Mov Disord* 2005; 20: 1255-1263; Emre et al. *Mov Disord* 2007; 22: 1689-1707). Typically, the prevalence of dementia in PD increases with disease duration: the 8-year cumulative prevalence of dementia reached 78% (Aarsland et al. *Arch Neurol* 2003;60:387-392) and 83% in a study with 20-year follow up of patients (Hely et al. *Mov Disord* 2008; 23: 837-844). This observation is in agreement with the presence of Lewy bodies in neocortex as described in Braak stages 5 and 6 (*Neurobiol Aging* 2003; 24: 197-211), but the pathophysiology of the cognitive deterioration in PD is complex and should consider other aspects: neuronal degeneration, involvement of neurotransmitters (acetylcholine, dopamine), presence of Alzheimer lesions, etc. (Rodriguez-Oroz et al. *Lancet Neurol* 2009; 8: 1128-1139; Kehagia et al. *Lancet Neurol* 2010; 9: 1200-1213).

More recent studies confirm the relatively high proportion of early PD patients who present cognitive impairment (Benito-León et al. *J Neurol Sci* 2011; 310: 176-182) although this decline apparently does not precede the diagnosis of PD (Sánchez-Ferro et al. *J Neurol Sci* 2011; 310: 211-215). In addition, it seems plausible that patients with early cognitive impairment are candidates to develop dementia over time due to progression of the deficits (Girotti et al. *J Neurol Neurosurg Psychiatry* 1988;51:1498-1502; Javin et al. *Mov Disord* 2006;21:1343-1349; Williams-Gray et al. *Brain* 2009;132: 2958-2969; Litvan et al. *Mov Disord* 2011; 26: 1814-1824). Factors associated to progressive cognitive impairment, such as older age, hallucinations, male gender, symmetry and severity of parkinsonism, non-tremor-dominant phenotype and presence of gastroenterologic and urologic disorders at baseline have been identified (Williams-Gray et al. *Brain*. 2007;130:1787-1798; Uc et al. *Neurology* 2009; 73: 1469-1477; Domellöf and Forsgren. *Mov Disord* 2011; 26: 2183-2189).

A wide variety of cognitive impairments has been recognized in PD, even in earliest stages of the disease, including memory, visuospatial function, attention, and executive function (Litvan et al. *Mov Disord* 2011; 26: 1814-1824). Interestingly, in a community-based study, 36% of patients newly diagnosed of PD and assessed in a detailed manner showed some evidence of cognitive impairment (Foltynie et al. *Brain* 2004; 127: 550-560). The definition of mild cognitive impairment (MCI) in PD remains debated and, therefore, some proposals have been made to establish the limits between normal and MCI on a continuum. Obviously, the sensitivity of the instruments applied for evaluating the cognitive state and the cutoff selected influence the detection of cases (Liepelt-Scarfone et al. *Parkinson Dis* 2011; 540843).

The type of MCI – defined as “cognitive decline that is not normal for age but with essentially normal functional activities” – most frequently found in PD is single domain and nonamnestic (Litvan et al. *Mov Disord* 2011; 26: 1814-1824).

Cognitive assessment in PD may be influenced by factors like age, motor difficulties, depression, and medication. Nonetheless, these factors have less weight in newly diagnosed patients, who can show cognitive impairment (19-30%) even before of starting the treatment (Aarsland et al. *Neurology* 2009; 72: 1121-1126; Elgh et al. *Eur J of Neurol* 2009; 16: 1278-1284). Cortical hypometabolism, particularly in posterior regions, has been demonstrated in drug-naïve PD patients with MCI and may be an early marker for later dementia (Pappatà et al. *Neurology* 2011; 77: 1357-1362).

Cognitive deterioration, even mild, has a negative effect on functional ability and quality of life (Young et al. *Mov Disord* 2010; 25: 2756-2761) and should be actively investigated and followed-up, due to its prognostic implications and impact. Caregivers can help in detection of MCI providing useful information (Naismith et al. *Mov Disord* 2011; 26: 161-164).