Letter to the Editor

Should patients with idiopathic rapid eye movement sleep behavior disorder receive preventive treatment for a neurodegenerative disease?

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To the Editor:

Neurodegenerative diseases are debilitating conditions that primarily affect the elderly population. Synucleinopathies (eg, Parkinson’s disease [PD], dementia with Lewy bodies, multiple system atrophy) involve accumulation of α-synuclein and abnormal intracellular Fe and protein transport, aggregation, and metabolism [1,2]. The neural degeneration in PD features abnormalities in the L-type Ca2+ channels of dopaminergic neurons and a consequent increase in oxidative stress and cell death. The elusive point in the treatment of neurodegenerative disorders is a desirable preventive intervention during the latent (preclinical) or prodromal (subclinical) phase. For this we need an appropriate diagnostic tool that allows for a sufficient advanced warning of an impending disease and a suitable neuroprotective agent.

Recent data suggest that centrally acting L-type calcium channel blockers (CCBs) of the dihydropyridine class may have protective role in the development of neurodegenerative diseases. The mechanism of action is the blockade of the voltage-gated calcium channels, which helps in reducing cellular iron overload, thus preventing protein aggregation, plaque formation, and consequent cell death [3-5]. Studies in humans suggest a neurodegenerative risk reduction (23%–40%) [6-9]. Methodological differences, such as pooling patients irrespective of the CCB class, may explain why some researchers could not find benefits [10-12].

Long-term use of CCBs might be a concern. However, life-threatening side effects are rare, and most of the other side effects predominantly present as systemic and site discomfort and nonlife–threatening cardiovascular symptoms. These reversible side effects are less frequent in the dihydropyridine class [13]. Thus, the potential risk for a long-term CCB treatment is reasonably low, particularly for hypertensive patients in whom such use presents an additional benefit. Conversely, in normotensive patients, blood pressure lowering is minimal, and other side effects even less prominent [14].

Therefore, should we give a dihydropyridine CCB to everyone over a certain age in absence of a simple predictive diagnostic test for a neurodegenerative disease? Although there is no simplediagnostic test, it is possible to predict the risk with certainty in a considerable number of cases, which is the instance for patients who present with REM sleep behavior disorder (RBD). The diagnostic test for RBD is polysomnography (PSG). Research shows that an idiopathic form of RBD (iRBD) can be predictive of various neurodegenerative diseases, including synucleinopathies [15-18]. The time span between the first diagnosis of RBD and the clinical onset of a neurodegenerative disease can be longer than 20 years, but it averages approximately 10 years [16,18]. In terms of prevalence, >65% of iRBD patients will eventually develop a neurodegenerative disorder [17], and it is estimated that 58% of patients with PD, >98% with dementia with Lewy bodies, and >95% with multiple system atrophy will suffer from a clinical or subclinical RBD [18].

Indeed, not all iRBD patients will rapidly evolve to synucleinopathy, and the factors underlying the variability of evolution are not fully understood. However, neuroimaging data showed that iRBD patients who evolved to a neurodegenerative disorder had prior patent abnormalities on dopaminergic imaging in the striatum or on transcranial sonography of the substantia nigra [19]. A recent study using single photon emission computed tomography demonstrated that iRBD patients with evolution to Parkinson disease or dementia with Lewy bodies had increased perfusion in the hippocampus at baseline, compared to RBD patients without evolution or to matched healthy controls [20]. These findings show that brain imaging may offer objective biomarkers identifying the best RBD candidates for preventative treatment, due to their high neurodegenerative risk.

Should we give dihydropyridine CCBs to patients with iRBD and high neurodegenerative risk and thus act preventatively before the clinical onset of a neurodegenerative disease? The answer seems (cautiously) affirmative until better agents are identified. Hypertensive patients with iRBD clearly would benefit from this preventative care.

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