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Perspectives

Rivastigmine for the treatment of dementia in patients with progressive supranuclear palsy: Clinical observations as a basis for power calculations and safety analysis

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Abstract Cognitive decline and dementia are present in about 50% of patients with progressive supranuclear palsy (PSP). Based on the known involvement of the cholinergic system in PSP patients, and because rivastigmine, in contrast to other cholinesterase inhibitors, inhibits both acetylcholinesterase and butyrylcholinesterase, we discuss clinical observations of five patients suffering from PSP and dementia who were all treated with rivastigmine over a period of 3 to 6 months. We found a slight improvement in specific cognitive function that may justify further controlled studies. A calculation of sample size revealed that a study on the effect of rivastigmine in PSP should include about 31 patients to detect a significant effect. In subtests, meaningful results can be obtained with even lower numbers (five patients for a verbal fluency test, and 14 patients for a logical memory task).

Keywords: PSP; Cholinesterase inhibitor; Dementia; Therapy

1. Introduction

Progressive supranuclear palsy (PSP), with an annual incidence of 5.3 new cases per 100,000 persons-year in the age range of 50 to 99 years [1], is a fairly rare, atypical Parkinsonian syndrome, with no treatment for ameliorating its inevitable progression or even alleviating symptoms. In addition to severe motor disturbances (which include the characteristic signs of vertical-gaze palsy and postural instability), the slowing of thought processes, frontal-lobe signs, memory disturbances, and difficulties in motor execution are core symptoms of a dementia that occurs in nearly half of all patients [2]. Behavioral disturbances, e.g., depression, disinhibition, or apathy, usually occur within the first year after disease manifestation [3,4].

2. Pathophysiological background and treatment of dementia in PSP

The etiologies of dementia and personality changes in PSP are only partly understood. Both cortical and subcortical alterations were discussed [5,6]. Dysexecutive frontal-lobe signs predominate, and are thought to be caused by deafferentation of the prefrontal cortex from the basal ganglia in PSP, which could be related to changes in cortical neurotransmitter systems.

The known alterations of the neurotransmitter system in PSP mainly involve the dopaminergic and cholinergic systems [7]. Degeneration of the dopaminergic, nigrostriatal system is thought to be related to some of PSP's Parkinsonian symptoms [8], whereas cholinergic deficits seem to be associated with the deterioration of cognition, similar to idiopathic Parkinson's disease (PD) or Alzheimer's disease (AD) [9]. Accordingly, several cholinergic regions, including the basal forebrain, parts of the basal ganglia, and mediodorsal thalamic nuclei, are affected in patients with PSP [8,10]. Moreover, acetylcholinesterase activity was shown to be decreased in these patients [11], but to a lesser extent compared with AD or PD [12,13]. In addition, neurons in the basal nucleus of Meynert are about 52% reduced, compared with healthy control subjects [14]. Cell loss of the basal nucleus of Meynert may also play a central role in the pathogenesis of cognitive disturbances in AD and PD. In PSP, cell loss also affects the pedunculopontine tegmental

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Table 1
Clinical characterization of PSP patients during baseline assessment

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	69	65	68	68	70
Sex	F	M	F	M	M
Duration of disease (months)	36	24	36	24	36
Symptoms					
Postural instability	+	+	+	+	+
Ophthalmoplegia	+	+	+	+	+
Bradykinesia	+	+	+	+	+
Rigidity	+	+	+	+	+
Dysarthria	+	+	+	+	+
Responsiveness to levodopa or apomorphine	Little	Little	None	Little	n.a.
Other neurologic symptoms	−	−	Dystonia	−	Positive pyramidal signs
Drug therapy					
L-dopa (mg/day)	400	300	850	300	−
Amantadine (mg/day)	−	−	300	−	−
Neuroleptics	−	−	−	−	Quetiapine
Sleeping pills	−	−	Hydroxycine, zopiclone	−	−
Antidepressants	Mirtazapine within first 3 months only	Venlafaxine-HCl	−	−	Mirtazapine within first 3 months only
Assessment					
Mini-Mental State Examination	23	23	21	18	26
Tower of London*	n.a.	38	2	3	35
CERAD: Verbal Fluency†	−2.54	−1.81	−1.44	−2.56	−1.76
CERAD: Boston Naming Test†	0.9	−0.96	0.13	−2.12	−1.74
CERAD: Praxis†	−3.17	−5.39	−4.76	−3.72	−3.57
WMS-R: Verbal Memory‡	57	65	65	49	58
WMS-R: Logical Memory I*	3	4	2	2	2
WMS-R: Logical Memory II*	37	4	22	1	4
WMS-R: Digit Span Forward*	15	20	76	28	15
WMS-R: Digit Span Backward*	5	11	13	2	9
Neuropsychiatric Inventory-10 total score	14	7	11	3	33
UPDRS-III score	30	42	33	32	36

Abbreviations: +, present; −, absent; F, female; M, male; n.a., not applied; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; WMS-R, German adaptation of Wechsler Memory Scale-Revised.

*Percentile rank scores.

†z-scores.

‡Index score (mean, 100; standard deviation, 15).

nuclei and other parts of the mesencephalic cholinergic cell groups [15,16].

These findings may lead to an assumption that cholinergic medication may be helpful for the treatment of specific aspects of dementia in PSP. However, the first reports of treatment with cholinesterase inhibitors (ChEIs) in patients with PSP and dementia were ambiguous. Physostigmine showed no consistent beneficial effects on cognitive function, although some patients slightly improved in various tasks testing long-term memory and attention [17–19]. Furthermore, two trials investigated the effect of donepezil, a longer-acting ChEI, on cognition in PSP patients [20], but had at best a modestly positive effect in the treatment of dementia [20,21]. On the other hand, one double-blind, placebo-controlled, randomized crossover trial detected a worsening in motor-related activities of daily living scales, whereas an open-label trial [21] registered no changes in motor performance and activities of daily living. No significant adverse events were recorded during the treatment phase with donepezil.

3. Rivastigmine in PSP: A case series of five patients

3.1. Methods

Based on the known involvement of the cholinergic system in PSP patients, and because rivastigmine, in contrast to other ChEIs, inhibits both acetylcholinesterase and butyrylcholinesterase, we treated five patients (Table 1) with PSP according to the National Institute of Neurological Disorders and Stroke and the Society for Progressive Supranuclear Palsy [4], and who fulfilled the Statistical Manual for Mental Disorders, Fourth Edition criteria of dementia, with the ChEI rivastigmine over a period of 3 to 6 months. Lacking any other treatment options, patients and their caregivers were told that treatment with rivastigmine was ''off label'' but could be attempted. All patients and their caregivers agreed to an individual test for a possible benefit of rivastigmine. Therefore, the dose of rivastigmine was individually adapted, according to the expected risk of side effects. All patients, except one