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Q1 Difficulties in the diagnosis of four repeats (4R) tauopathic parkinsonian syndromes

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1. Introduction

Corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) belong to atypical parkinsonisms (APS) which due to their histopathology are defined as primary tauopathies [1–7]. In the classification of tauopathies PSP and corticobasal syndrome (CBS) are most commonly associated with tau proteins containing four repeats (4R) of approximately 32 aminoacids in the microtubule binding domain [1–3]. Nevertheless regarding the fact that CBS may be related to 4R pathologies such as CBD and PSP, but also Alzheimer's disease (AD) and Pick's disease which are associated with three repeats tauopathies (3R), it should be stressed that CBS may be a clinical manifestation of either 3R or 4R [7]. It should also be highlighted that AD may be related to accumulation of both 3R and 4R [7]. This is one of the aspects allowing neuropathological differentiation between CBD/PSP and frontotemporal lobar degeneration, which is related with three repeats (3R). PSP and less common CBD were described in 1960s (PSP in 1964, CBD in 1968) [4–7] as neurodegenerative diseases with relatively short duration and rather difficult differentiation from each other and other extrapyramidal disorders [4]. PSP and CBD due to their similar symptomatology and pathology are often mistaken with each other. Often patients have symptoms characteristic for both diseases.

The aim of the study was to discuss whether strict differentiation of most likely CBS and PSP is justified in all cases. Clinical presentations were correlated with mental dysfunction and neuroimaging.

2. Material and methods

Five patients with clinical symptoms combining CBS and PSP were assessed. In this study generally accepted criteria of diagnosis of CBD and PSP were used [5,6] (Tables 1 and 2). The presence and stage of ocular motor dysfunction, postural instability, akinesia and cognitive dysfunction were used as basic criteria of the most common subtype of PSP – Richardson syndrome. The certainty of diagnosis was based on the intensity of symptoms. (Table 1). CBD was examined by assessing the presence and stage of apraxia, alien limb phenomena, cortical sensory loss, cognitive impairment, behavioral changes, and aphasia, asymmetric onset of

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Table 1 – Corticobasal degeneration – criteria* [5].

Diagnosis/symptoms	Limb rigidity of akinesia	Limb dystonia	Limb myoclonus	• Orobuccal or limb apraxia • Cortical sensory deficit • Alien limb phenomena (more than simple levitation)	Other
Possible CBS (clinical presentation may be symmetric)	1 of mentioned above symptoms			1 of mentioned above symptoms	–
Probable CBS (asymmetric)	2 of mentioned above symptoms			2 of mentioned above symptoms	–
CBD-PSP	*	*	*	*	* – 3 of: (a) axial or asymmetric limb rigidity or akinesia (b) postural instability or falls (c) urinary incontinence behavioral changes (d) supranuclear vertical gaze palsy or decreased velocity of vertical saccades

Based on Ref. [5].

Table 2 – Progressive supranuclear palsy [6].

Level of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
1 (highest)	Vertical supranuclear gaze palsy	Repeated unprovoked falls within 3 years	Progressive gait freezing within 3 years	Speech/language disorder i.e. nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech
2	Slow velocity of vertical saccades	Tendency to fall on the pull-test within 3 years	Parkinsonism, akinetic-rigid predominantly axial and levodopa resistant	Frontal cognitive/ behavioral presentation
3 (lowest)	Frequent macro square wave jerks or ''eyelid opening apraxia''	More than two steps backward on the pull-test within 3 years	Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	Corticobasal syndrome

Based on Ref. [6].

levodopa-resistant parkinsonism, dystonia, and myoclonus. The more symptoms were present in the clinical examination, the more certain the diagnosis was (Table 2). Symptoms of both diseases were observed among all patients demonstrated in the study. The inclusion and exclusion criteria of both diseases were assessed. In this work 5 case studies of patients with insufficient symptomatology to diagnose either CBD or PSP are demonstrated (Table S1). All of these patients were examined by neurologists experienced in movement disorders – (AF, DK). Psychological examinations were performed using Montreal Cognitive Assessment (MoCA) or Mini Mental State Examination (MMSE) and Frontal Assessment Battery (FAB). Neuroimaging was performed using magnetic resonance imaging (MRI) and single photon emission computer tomography (SPECT). The project was approved by the Ethical Committee of the Medical University of Warsaw – AKBE243/2016.

3. Study

3.1. *Patient #1*

A 82-year-old female patient was admitted to the Department of Neurology in November of 2016. Since 2012, when she was 78 years old, the patient's family observed slowness of speech, psychomotor slowness and falls. At the time of the examination the patient presented facial masking, oculomotor apraxia, paresis of the right upper and lower limb. Bradykinesia was more visible on the right side of the body than on the left. Patient presented more severe bradykinesia in lower limbs than in upper ones, general psychomotor slowness, retropulsion and lack of balancing during gait. The patient complained of deterioration of handwriting, memory deficits, symptoms of orthostatic hypotension, constipation, dysuria and abnormal sweating. Logopedic examination demonstrat-

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