When Parkinsonism Deceives: A Case of Leukodystrophy Masquerading as PSP

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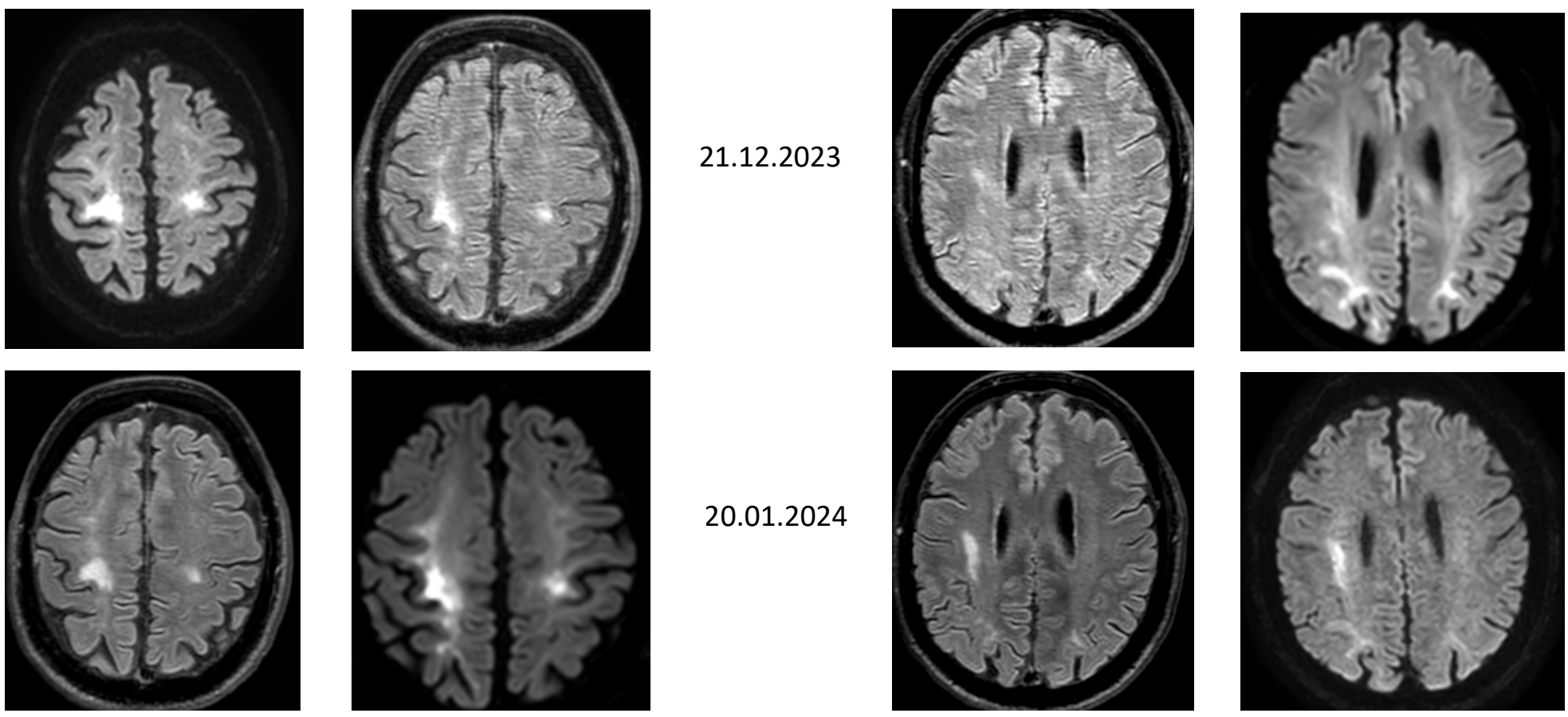
Introduction: Progressive supranuclear palsy (PSP) is a neurodegenerative disease that may present with a variety of motor and non-motor symptoms, including postural instability, supranuclear gaze palsy and cognitive impairment. The disease is usually sporadic, but a number of genetic conditions may mimic PSP[2], so reasoned application of the diagnostic criteria[1] is required
We present a patient diagnosed with PSP according to current criteria disclosing atypical findings on neuroimaging (magnetic resonance, MRI).

Clinical history: A 62-year-old man presented with a 7-year history of **progressive bradykinesia** and **axial rigidity**. He had no relevant medical or family history. Early investigations, including brain MRI and ^123I-ioflupane SPECT, showed a **right centrum semiovale infarct** and bilateral dopaminergic deficit, leading to a diagnosis of Parkinson's disease. Dopaminergic therapy was poorly tolerated and minimally effective. Over time, he developed progressive gait impairment with **severe postural instability, recurrent falls, urinary urgency**, constipation, nocturnal akinesia, and sleep disturbances.
Neurological examination revealed a stooped posture with absent arm swings, axial rigidity, start hesitation, and postural instability. Moreover, symmetric bradykinesia and rigidity (worse in the lower limbs), mixed tremor (predominantly left-sided), brisk reflexes, and oculomotor signs (**marked upward gaze palsy, moderate downward limitation, hypometric horizontal saccades**) were noted. Routine blood analysis, abdominal ultrasound, and orthostatic testing were unremarkable. L-DOPA challenge confirmed poor responsiveness. Cognitive testing showed borderline global cognition (MMSE 25.2/30; MoCA 23.98/30), with selective attention and working memory deficits.
Brain MRI with gadolinium revealed **bilateral fronto-parieto-occipital asymmetric white matter changes**, with **peripheral diffusion restriction** and no enhancement. The pattern remained stable over time and was **suggestive of a leukodystrophy**, particularly of the **hereditary diffuse leukoencephalopathy with spheroids (HDLS)**, a rare condition related to CSF1R mutations[3]. A leukodystrophy gene panel only identified a variant of uncertain significance in the ASXL2 gene (c.3194A>G; p.(Gln1065Arg), classe 3, ACMG).



Discussion: The clinical picture was highly suggestive of PSP, but both the neuropsychological profile and MRI findings were suggestive of a leukodystrophy. Genetic panel was not resolutive, and genome-wide sequencing is undergoing. Previous MRIs misinterpreted DWI restriction as strokes, even though the persistent DWI restriction should have suggested an alternative diagnosis.
Conclusions: The diagnosis of PSP is a clinical challenge in the field of movement disorders and a cautious review of clinical history, imaging and neuropsychological assessment is mandatory before establishing a diagnosis.

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