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Distinguishing PLS from Parkinsonian syndromes with the help of advanced imaging

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Part one

Abstract

We describe a unique case of a patient presenting with unilateral mild paresis, slowing of the upper limb and parkinsonism and a full imaging work-up including MR, 123I-FP-CIT, 18F-PE2I and 18F-FDG. This case demonstrates that imaging may aid substantially in the diagnostic work-up of complex neurological disorders.

Case study

We report a case of an adult 60-year old male patient that initially presented after six months with subacute and slowly progressive symptoms including muscle stiffness, decreased fine motor skill, slowing of movements and mild muscle weakness of his right hand. Patient was right-handed and experienced writing difficulties – without cramps or dystonia – that affected legibility. He had no complaints of postural symptoms associated with orthostatic hypotension or other autonomic failure. No sleep disturbance, periodic limb movement of sleep, nor restless legs syndrome was mentioned.

The patient had a history of a myocardial infarction, diabetes mellitus and hypercholesterolemia; the latter two were relatively well controlled with medication. His family history was negative for neurodegenerative diseases.

The neurological examination showed slowness in whole-hand grasping and on tapping tasks, and mild paresis of dorsal interosseous muscles of the right hand. Furthermore, we found an asymmetrical mild hypertonia in lower right limb. A unilateral positive Hoffman's sign (right) was noted, but we found no Babinski sign and tendon reflexes were symmetrically brisk. During walking we observed a reduced arm swing on the right side without postural imbalance or gait disorder. There was no evidence of myoclonus. All sensory modalities were normal. The eye movements, both saccades and vertical gaze, were normal. Furthermore, detailed language testing and behavioral assessment showed no abnormalities. Obtaining a diagnosis remained challenging as it was difficult to distinguish between parkinsonism or a motor neuron disorder.

Hematological and serum biochemistry tests were normal. Electromyography was strictly normal.

Magnetic resonance imaging (MRI) of the brain demonstrated mild white matter lesions normal for his age, without any hyperintensity in the corticospinal tracts. The cervical MRI showed no evidence of myelopathy / radiculopathy. 18F-FDG brain PET showed asymmetric mild hypometabolism in the left sensorimotor cortex compatible with the right arm symptoms, in favor of a motor neuron disease. To exclude neurodegenerative parkinsonism 123I-FP-CIT SPECT was performed nine months later and showed normal presynaptic dopaminergic transmission (Figure 1).

Notably, there was no response to dopaminergic treatment with levodopa/benserazide.

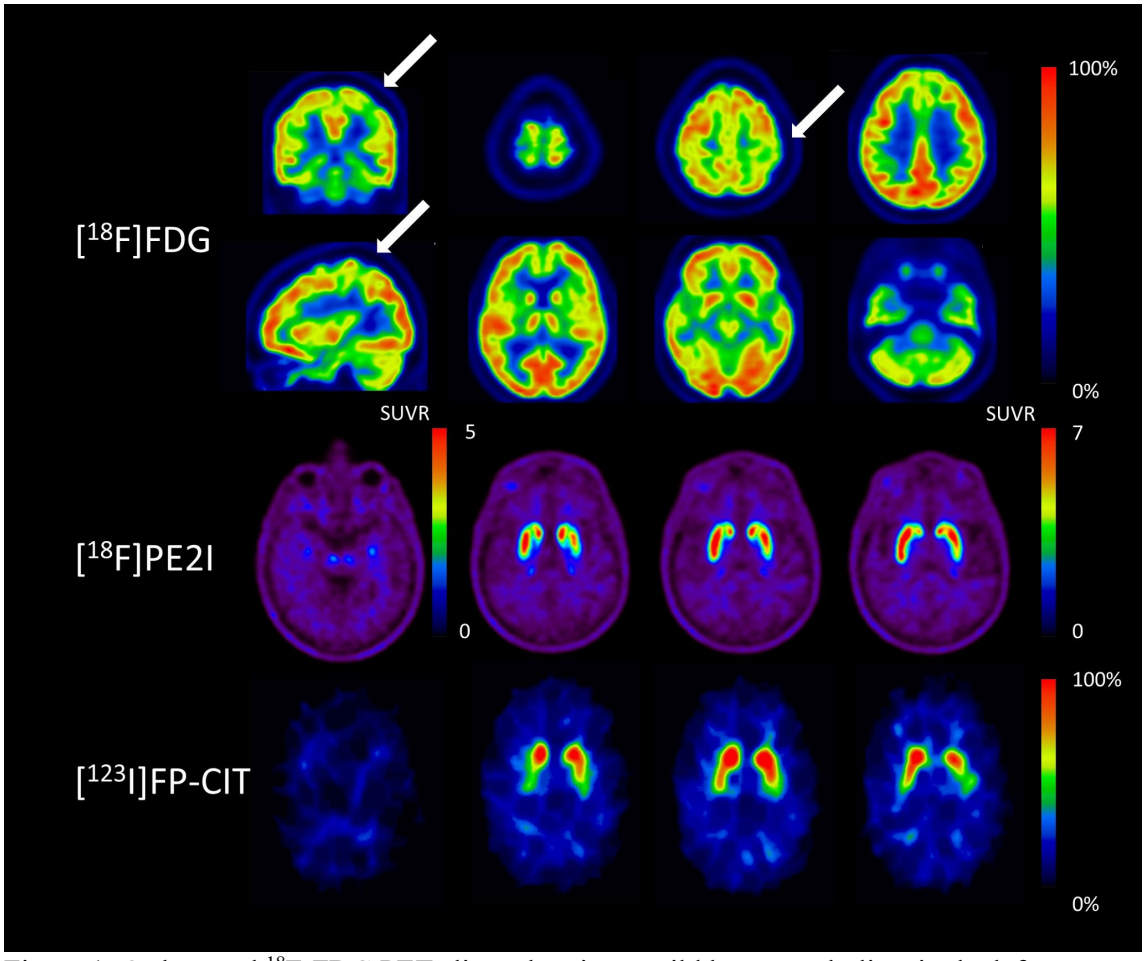

Figure 1: Orthogonal ^{18}F-FDG PET slices showing a mild hypometabolism in the left sensorimotor cortex corresponding to the right arm location of the cortical homunculus. Middle and bottom row: transverse slices of dopamine transporter imaging. Both classical ^{123}I-FP-CIT SPECT and high resolution, selective ^{18}F-PE2I PET showed a normal presynaptic dopaminergic uptake. Images are in radiological orientation.

Discussion section

Differential diagnosis was broad. After excluding structural disorder, metabolic, inflammatory and infectious disorders, the diagnosis was leaning towards a motor neuron disorder. Finally, we found no mutations in the SOD1, TARDBP, FUS or C9orf72 genes. Whole exome sequencing was done but showed no mutations related to neurodegenerative disorders.

Besides a slow progression of isolated paresis of the right hand, patient's condition remained unchanged during a one-year follow-up period. Repetition of the EMG showed no signs of lower motor neuron degeneration. We requested a more sensitive 18F-PE2I PET scan to exclude subtle presynaptic dopaminergic transmission deficits. This imaging showed no abnormalities in the striatum, nor in the substantia nigra.

Part two

Final diagnosis

Together, the clinical picture and ancillary tests were compatible with an asymmetric form of pure upper motor neuron disorder. The imaging allowed the diagnosis of Primary lateral sclerosis (PLS) by showing on the one hand a hypometabolism of the sensory-motor cortex controlateral to the clinical involvement, and on the other hand a presynaptic integrity of the dopaminergic pathways.

Conclusion

PLS, is a rare neurodegenerative disorder, characterized by a slowly progressive upper motor neuron (UMN) syndrome. Compared to classical variants of amyotrophic lateral sclerosis, PLS has a significantly slower rate of disease progression and longer survival. Diagnosis of PLS is challenging and is based on excluding structural disorders (e.g. cervical spondylotic myelopathy, Arnold-Chiari malformation, spinal arteriovenous fistula, tumor), hereditary spastic paraparesis (HSP), leukodystrophies, metabolic and toxic disorders (e.g. vitamin E deficiency, cerebro-tendinous xanthomatosis, hexosaminidase deficiency), neurodegenerative disorders (e.g. Parkinson disease, multiple systems atrophy, corticobasal syndrome), inflammatory (e.g. primary progressive multiple sclerosis) and infections (e.g. neurosyphilis, tropical spastic paraparesis, neuroborreliosis, spinal sarcoidosis, AIDS). Thalamic, hippocampal and basal ganglia atrophy, and subcortical grey matter degeneration have been demonstrated in imaging studies of PLS (1). Post-mortem studies reported atrophy of the thalamus and striatum, as well as TDP-43 inclusions in striatum, amygdala, hippocampus and basal ganglia.

In this case, molecular imaging had a substantial added value to aid in the differential diagnosis between neurodegenerative parkinsonian syndromes and amyotrophic lateral sclerosis. Neurodegenerative parkinonian syndromes are characterized by presynaptic dopaminergic deficit . 123I-FP-CIT SPECT is widely used in clinical practice to visualize the dopaminergic system integrity at the level of the presynaptic terminals in the striatum (2). 18F-PE2I PET is a novel highly selective and high-resolution DAT imaging technique that allows visualization and quantification of both the striatum and the substantia nigra (3). As both techniques repeated after twelve months follow-up were normal, a presynaptic dopaminergic deficit could be excluded. Although dopaminergic deficits have been described in amyotrophic lateral sclerosis patients, a recent report in PLS patients with atypical signs of parkinsonism did not find any dopaminergic deficits (4), in line with our results.

Moreover, also 18F-FDG PET showed typical signs of a motor neuron disease as a mild hypometabolism in the left sensorimotor cortex was found corresponding to the right arm location of the homunculus (5, 6). Therefore, advanced brain imaging enabled to guide the diagnosis.

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