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Case report

Progressive dopaminergic defect in a patient with primary progressive multiple sclerosis

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ABSTRACT

Dopamine has a modulatory role in a number of autoimmune diseases, but there are no published cases of longitudinal dopaminergic imaging in multiple sclerosis (MS). Here we report a patient with primary progressive multiple sclerosis (PPMS) who was scanned twice with brain dopamine transporter single photon emission computed tomography (SPECT) with an interval of four years. The results showed a loss of tracer binding that corresponded to a 4–7 fold steeper decline than in normal ageing. The finding points to a relevant role of nigrostriatal dopaminergic degeneration in the pathological process of PPMS.

1. Introduction

In approximately 15% of patients with multiple sclerosis (MS), the disease course is progressive starting from onset (primary progressive MS, PPMS). (Correale et al., 2017) The pathogenesis of PPMS is largely unknown but a dynamic interplay between neurodegeneration and neuroinflammation is apparent. (Correale et al., 2017) Dopamine is a monoamine neurotransmitter that is not classically considered to be particularly important for MS, although there is accumulating evidence of a modulatory role of dopamine in a number of autoimmune diseases. (Pacheco et al., 2014) However, to date, dopamine neurotransmission has not been longitudinally investigated in MS with *in vivo* brain imaging.

In this study, we present a patient who developed an asymmetrical gait disorder and was diagnosed with PPMS. Along with other diagnostic measures, the patient was scanned twice with brain dopamine transporter (DAT) SPECT. The imaging results demonstrated clearly reduced striatal dopaminergic function and a considerably greater annual loss of DAT binging than in normal ageing. The case represents the first reported MS patient scanned repeatedly with functional dopaminergic brain imaging.

2. Case report

A 44-year-old man presented with right lower limb muscle stiffness and weakness. Initial examinations for the patient included CNS MRIs and electroneuromyography. The only abnormal finding was a slightly increased signal in cervical spine MRI at the level of the 4th vertebrae, but the lesion was considered unspecific and not clearly abnormal. Symptoms progressed during the next year, and MRI-examinations were repeated with unremarkable findings. CSF at the time of initial examination showed a single oligoclonal fraction not detectable in serum, normal leukocyte count, and slightly elevated protein, albumin and IgG levels; however, IgG index was normal. Due to unclear progressive gait disorder and a family history of Parkinson's disease (PD, mother), a DAT SPECT scan was performed, which revealed a mild loss of dopaminergic function (−1 to −2 SDs from the normal range) (Fig. 1D). Brain [^{18}F] fluorodeoxyglucose PET (Fig. 1C) and a whole exome sequencing (Fulgent Genetics, Temple City, CA) were also performed with no pathological findings or mutations. The patient received physiotherapy which was partially beneficial and was treated with levodopa, biperiden, baclofen, selegiline, pramipexole, rotigotine and rasagiline without positive response.

Due to symptom progression and mildly abnormal binding in the first DAT scan, the patient was scanned again four years after the first

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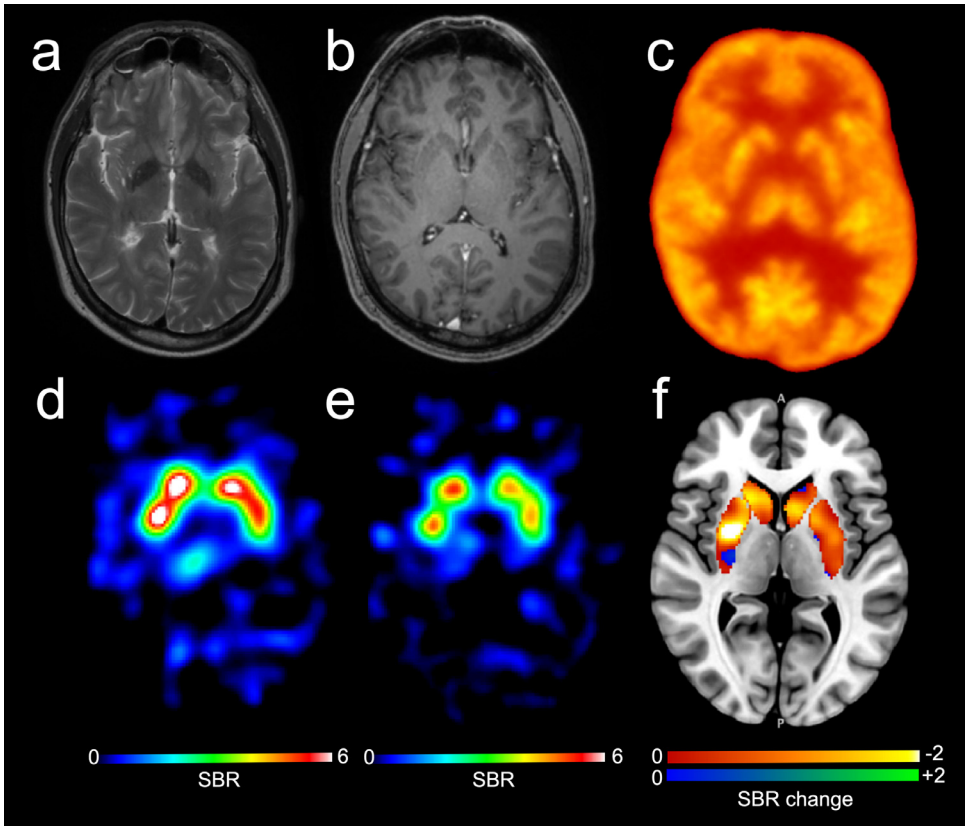

Fig. 1. Progressive loss of striatal dopamine function in PPMS without structural or metabolic abnormalities in the striatum.
Brain MRI scanning showed no striatal abnormalities in T2- or T1-weighted sequences (panels A and B; scanning performed after the second DAT SPECT). In addition, [^{18}F]fluorodeoxyglucose PET was normal (panel C). The first [^{123}I]FP-CIT SPECT scan showed mild patchy losses of DAT binding (panel D). In the second DAT scan four years later (panel E), the dopaminergic defect had progressed by 13–26% (a 4–7 times faster rate than that expected due to normal ageing). The defect was not uniform across putaminal subregions and there was also marked decline in the caudate nuclei (panel F, difference in SBR between the scans overlaid on the MNI152 template). Striatal specific binding ratios (SBRs) were calculated relative to the occipital cortex (SBR = [striatal region – occipital cortex]/occipital cortex).

scan. The second DAT scan showed clear 13–26% reduction in tracer binging which corresponded to a 3.3–6.5% annual decline in all regions (0.9% in normal ageing (Karrer et al., 2017))(Fig. 1E). MRI scanning was repeated and showed typical periventricular MS lesions in the brain as well as multiple chronic lesions in the cervical spine, without striatal abnormalities (Fig. 1A). When the earlier MRI was re-evaluated, similar but considerably less numerous and prominent lesions were observed that had not been identified at the time of scanning. The patient received a diagnosis of PPMS according to the McDonald 2017 diagnostic criteria (Thompson et al., 2018). This was based on symptom progression, several periventricular, one infratentorial, and several spinal cord lesions consistent with demyelination, together with the exclusion of other causes. The patient is currently receiving treatment with ocrelizumab.

3. Discussion

PPMS may go unrecognized for some time with a delay in diagnosis. (Correale et al., 2017) Our case was scanned twice with DAT imaging because the diagnosis remained unclear, partly due to misreading of MRIs. The patient had a gait disorder but no tremor, rigidity or bradykinesia and the whole exome sequencing was normal without any pathological mutations. As a result of repeated SPECT scanning, a progressive degeneration of the nigrostriatal tract was documented that was robustly 4 to 7-fold faster than that in normal ageing. Although there are anecdotal reported cases of coexistant MS and PD (Valkovic et al., 2007), there are no previous reported cases of longitudinal functional dopaminergic brain imaging in MS or PPMS. In PD, a condition characterized by a progressive degeneration of the nigrostriatal tract and loss of dopamine, there are relevant autoimmune mechanisms in the pathological process. (Sulzer et al., 2017) It is of interest to note that the distribution of the striatal dopaminergic loss in our PPMS case appears different from PD. While PD is associated with an asymmetric and predominantly posterior putaminal loss of presynaptic dopaminergic function, (Kaasinen and Vahlberg, 2017) PPMS showed more symmetrical, widespread and patchy reduction in DAT binding.

There is some *in vitro* evidence of potential benefit of dopaminergic drugs in MS (Marino and Cosentino, 2016), that may be mediated not only by the effects on peripheral immune cells but also by direct effects on brain cells of innate immunity. (Pinoli et al., 2017) A dopaminergic drug treatment was tested for our patient, but levodopa or other dopaminergic medications did not alleviate symptoms. It is possible that it is not the loss of dopamine but the prominent axonal damage in PPMS, (Petzold et al., 2005) that is reflected in the accumulating dopaminergic defect. This neurite loss could be relatively resistant to symptomatic dopaminergic drugs.

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Declaration of Competing Interest

Authors declare no conflicts of interest.

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