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# Co-morbid demyelinating lesions and atypical clinical features in a patient with Parkinson's disease

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The co-occurrence of Parkinson's disease (PD) in association with Multiple Sclerosis (MS) has been reported occasionally [1,2] (see Table 1). As advanced age is one of the few risk factors for PD, with longer life expectancy MS patients could be at risk of developing PD [3]. We report clinic-pathologic findings in a PD patient with atypical clinical features in whom co-existing demyelinating lesions were detected at postmortem evaluation.

A 58-years old diabetic man started, after a severe depression, with clumsiness and irregular rest tremor on the right hand. Over the years, the patient developed severe gait disturbance with freezing, and REM sleep behavior disorder. Shortly thereafter, the patient developed urinary incontinence. Response to levodopa treatment was overall poor and associated with mild to moderate dyskinesias, but without motor fluctuations. His first assessment at our Movement Disorders Clinic was 12 years after the onset of symptoms. On neurological exam, he presented symmetric bradykinesia, postural tremor in upper limbs, moderate axial and limb rigidity, wide-based gait with freezing and severely affected postural reflexes. In addition, pyramidal signs were observed with left Babinski sign; extraocular movements were normal. He complained about memory problems and he scored 17/30 in the Mini-Mental State Examination. Brain magnetic resonance imaging (MRI) showed global cortical atrophy, a left parietal encephalomalacia area and periventricular white matter (WM) (Fig. 1A) and basal ganglia lesions suggestive of small vessel disease (SVD). Demyelinating lesions were initially not detected by MRI. Dopamine transporter imaging showed severe decreased uptake in caudate nuclei and putamina (Fig. 1O) confirming the presence of presynaptic dopaminergic dysfunction. No lumbar puncture was performed.

As the disease progressed his motor and cognitive functions deteriorated, he was wheelchaired and became apathetic. He died at age of 75 of respiratory insufficiency, and family consented brain donation at the IDIBAPS Brain Bank. Unfixed brain weight was 1395g. Gross examination showed mild global cortical atrophy, and moderate depigmentation of substantia nigra and locus coeruleus. Besides, an ill-defined, greyish cortico-subcortical lesion suggestive of demyelination was detected in the right parietal lobe. Histological examination showed α-synuclein immunoreactive Lewy-type pathology involving pigmented brainstem nuclei, limbic system, insula and frontotemporal cortex corresponding to Braak stage 4 of PD-related pathology (clone KM51, Novocastra). In addition, Tau-positive (AT8, Thermo Scientific) neurofibrillary pathology in limbic areas and sparse cored amyloid plaques were observed. SVD and small lacunar infarct in frontal WM, without involvement of basal ganglia, were also found. Moreover, demyelinating lesions were observed in several brain areas. A large leukocortical, well-delineated hypocellular demyelinated lesion was found in the right parietal cortex (corresponding to the gross lesion), involving deep cortical layers, underlying arcuate fibers and WM (Fig. 1G-L). Further extensive demyelinating lesions were found in occipital and entorhinal cortices, and smaller ones in the following areas: insular cortex, corticosubcortical boundary of the motor cortex, frontal WM,

**Table 1**
Literature overview of co-incident PD and MS.

| Reference | *n* | Diagnosis (P/L)* | Age of PD/PS onset | NP | Hypothesis | PD/PS diagnosis based on | Response to MS/PD treatment |
|---|---|---|---|---|---|---|---|
| Pedemonte et al. | 7 | MS/PS | 39-73y** | no | coincidental | DAT scan | only levodopa response was described |
| Damasio et al. [6] | 1 | MS/PD | 38y | no | coincidental | DAT scan | no |
| Valdovic et al. | 1 | PD/MS | 36y | no | coincidental | DAT scan | no |
| Etemadifar et al. [7] | 8 | MS/PD | 30-55*** | no | coincidental | clinical symptoms | unknown |
| Barum et al. [8] | 2 | MS/PD | 39, 56 | no | coincidental | DAT scan | good response to corticosteroid and levodopa |

* P- presenting symptoms; L-late symptoms; **ages: 39y, 56y, 63y, 71y,73y; **ages: 30y,31y,39y, 43y, 44y, 55y.
PS- Parkinsonian syndrome; PD- Parkinson's disease; NP- Neuropathological evaluation; DAT scan-dopamine transporters scan.

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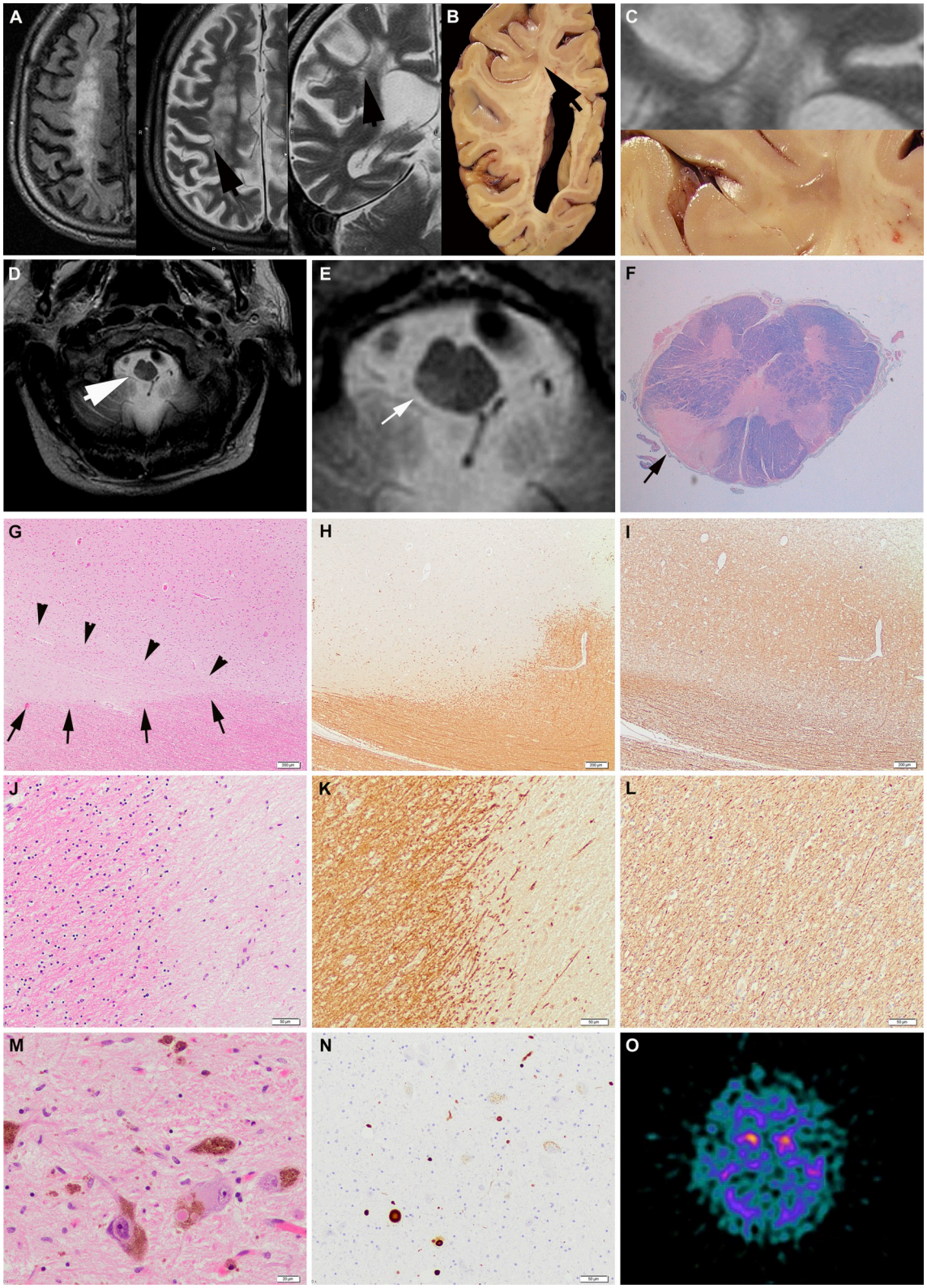


**Fig. 1. A-C**: side-by-side MR and gross brain images showing a right parietal, cortico-subcortical lesion (black arrows in A and B), which is better appreciated at higher magnification (C), corresponding to the histologically confirmed chronic inactive demyelinating lesion. **D-F**: hyperintense lesion in right bulbomedullary transition/upper cervical cord (white arrows in D and F), which is also well identified at postmortem study by luxol-fast-blue stain (F, arrow). **G-L**: histological features of one of the chronic inactive demyelinating lesions characterized by a well delineated, cortico-subcortical, hypocellular plaque (G and J; H&E stain), with complete absence of myelin sheaths (H and K; anti-MBP immunohistochemistry) and relative preservation of axons (I and L; anti-neurofilament immunohistochemistry). **M-O**: PD-related pathology characterized by the presence of Lewy-bodies in pigmented neurons of substantia nigra (M, H&E stain), immunoreactive for alpha-synuclein (N; anti-alpha-synuclein immunohistochemistry). Dopamine transporter (DAT) imaging performed during life revealed decreased uptake in both caudate nuclei and putamen (O). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

subventricular region of medulla oblongata, and in spinal cord affecting substantia gelatinosa and cuneate fasciculus (Fig. 1). In all lesions there was a selective loss of myelin sheaths (by luxol-fast-blue stain and myelin-basic-protein immunohistochemistry), relative preservation of axons (by neurofilament immunohistochemistry), with only few residual macrophages without inflammatory infiltrates (Fig. 1). Additionally, myelin-basic-protein immunostaining showed extensive cortical demyelination of the temporal, parietal and occipital lobes. These lesions were consistent with chronic inactive demyelinating plaques along with diffuse cortical demyelination.

The co-existence of PD and MS in one individual is rare and has been estimated to occur in 1 individual per 500.000 [3]. In only one report, one patient developed parkinsonism before the clinical diagnosis of MS [1]. The risk of PD among patients with MS seems to be low or absent [3]. This association could be mere chance, due to the increasing frequency of Lewy-type pathology with aging. Despite evidences supporting a co-incidental association, recent studies have focused on genetic aspects of the relationship between MS and PD [4,5]. A genetic variability of HLA-DRB5 has been given a role in inflammatory aspects of both [4,5].

The role of demyelinating lesions and their relationship with PD is unclear in our case. Different possibilities arise. First, an acute reversible parkinsonism could appear in a patient with relapsing-remitting MS secondary to a new demyelinating lesion in a strategic location (globus pallidus, thalamus, substania nigra and nucleus ruber), often steroid-responsive. Moreover, a demyelinating lesion occurring at a presynaptic level, i.e. substantia nigra could also alter the dopamine transporter imaging (DAT scan). However, no such lesions were observed in our patient and clinical evolution did not support RR-MS. Second, a gradual and progressive parkinsonism could represent one symptom of primary or secondary progressive MS involving the basal ganglia, but this was also not observed at postmortem investigation. Lastly, and probably the most likely situation in the present case, a coincidental primary neurodegenerative parkinsonism coexisting with unrelated MS. A family history of autoimmune disease was not known. As there was no clinical history suggesting a demyelination “attack” or a monophasic post-viral or post-vaccination event, no clinical evidence of episodic worsening during the follow-up, and no demyelinating lesions detected in basal ganglia or s. nigra at postmortem investigation, the lesions could be considered to have been relatively “silent” corresponding to a radiologically/neuropathologically isolated syndrome. However, MS-type plaques may have influenced the severity of the patient's PD symptoms, the poor response to antiparkinsonian drugs (anticholinergic, L-Dopa, rasagiline), and also other atypical symptoms, such as pyramidal signs and the early urinary incontinence [3]. The presence of small vessel disease could have also contributed, at least partly, to some of the described atypical symptoms. Furthermore, the extensive cortical demyelination, which is a contributing factor for dementia in MS, and the lesions in the entorhinal region might have also contributed to the behavioral and cognitive symptoms. This may hold true also for the coexistence of Alzheimer type pathology in limbic areas. Sensory symptoms that might have been attributed to the demyelinating lesion in the substantia gelatinosa of the spinal cord were not reported. A Parkinson-plus syndrome could have justified some atypical features. However, clinical criteria for dementia with Lewy bodies or neuropathological features of e.g. multiple system atrophy or progressive supranuclear palsy were not observed.

In sum, we present a patient with clinical, imaging and neuropathological findings characteristic of PD with concomitant extensive demyelinating plaques, microvascular brain lesions and mild AD-pathology. The co-occurrence of the MS-like pathology may have been coincidental, but we consider that its presence might have contributed to the poor outcome and atypical clinical features. The presence of atypical features in patients with PD should entail additional investigations even though presented in a later disease stage. To our best knowledge this is the first postmortem description of both pathologies in a patient with clinical PD diagnosis.

## Author contribution

RR-D wrote the manuscript. EG and RR-D conducted the neuropathological study. DV and NB reported the clinical history. ET and EG planned the study, reviewed the manuscript and they are responsible for the overall content.

## Potential conflict of interest

None.

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## Disclosures

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