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Levodopa response and motor fluctuations in beta-propeller protein-associated neurodegeneration.

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Abstract:	We report on a case of BPAN presenting levodopa-responsive dystonia parkinsonism syndrome, associated with early motor complications. The observation of severe levodopa-induced motor complications is uncommon in taupathies and might be a disabling feature in BPAN, especially in those patients with prominent iron accumulation in the substantia nigra rather than the striatum.
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Dear Editor,

On behalf of all the authors, I would like to submit the manuscript entitled: “Levodopa response and motor fluctuations in beta-propeller protein-associated neurodegeneration”.

Motor fluctuations and dyskinesias represent the major complications of the long-term therapy with levodopa in Parkinson’s disease. Similar motor complications may also be observed in other conditions associated with substantia nigra neuronal loss.
Here, we report on a case of BPAN presenting adulthood progression with development of levodopa-responsive dystonia parkinsonism syndrome, associated with prominent and early motor complications. This might be due to the severe dopaminergic depletion in the striatum as assessed by DAT imaging and the prominent involvement of the substantia nigra by iron accumulation, whereas the striatum was less affected. The observation of severe levodopa-induced motor complications is uncommon in taupathies and might be a disabling feature in BPAN, especially in those patients with prominent iron accumulation in the substantia nigra rather than the striatum.

All authors have approved the final article. We confirm that the paper has not been previously published, it is not under simultaneous consideration by another journal and no ghost writing by anyone not named on the author list must be included. We have received a signed release form from the patient videotaped authorizing the offline and/or online distribution of the video material.
The authors report no conflicts of interest.
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We hope you will consider also this manuscript to be reviewed by the Editorial Board.

Sincerely,

Dr. Antonio Emanuele Elia

Video is part of ms

Levodopa response and motor fluctuations in beta-propeller protein-associated neurodegeneration.

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Ethical Compliance Statement:

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The patient has given written and informed consent for online publication of her video. The authors confirm that the approval of an institutional review board was not required for this work.

Motor fluctuations and dyskinesias represent the major complications associated with levodopa in Parkinson's disease (PD). We report on a case of beta-propeller protein-associated neurodegeneration (BPAN) presenting with a young-onset levodopa-responsive dystonia parkinsonism, who developed early motor complications after the initiation of levodopa.

The patient is a 34-year-old right-handed lady, who was referred for a 2-year history of progressive slowing of movement associated with episodes of "spasms" affecting the left leg. She gradually developed clumsiness of the left limbs, cognitive decline and social isolation. Her parents reported sleep talk and screaming at night, and the presence of excessive movements during sleep.

She was diagnosed with a young-onset parkinsonism and started levodopa+benserazide titrated up to 100+25 mg four times/day, with significant improvement in motor function. Nevertheless, after only four months, she developed early mild motor fluctuations and dyskinesias.

Over the course of the last four years, motor complications progressed into disabling OFF-periods, characterized by severe bradykinesia, and troublesome peak-dyskinesias (causing a weight loss of about 10 kg) and requiring a reduction of levodopa therapy. Generalized dyskinesias significantly impaired walking and daily activities (video).

Brain MRI disclosed bilateral T2* hypointensity in the globus pallidus and in the midbrain, involving the substantia nigra. Dopamine transporter (DAT) tomography showed a bilateral reduced uptake in the striatum (figure). Genetic screening revealed a never described and *de novo* c.344+2T>G mutation in the WDR45 gene. Neuropathological investigation on cerebrospinal fluid (CSF) samples disclosed reduced levels of β-amyloid 1-40 [5226 pg/ml (7755-16715)] and β-amyloid 1-42 [500 pg/ml (> 640)]. Conversely, Aβ1-42 / Aβ1-40 ratio [0.096 pg/ml (0.068-0.115)], t-tau [254 pg/ml (146-404)] and p-tau levels [23.4 pg/ml (21.5-56.5)] were within the reference range, and 14-3-3 protein was not found.

BPAN is a neurological disorder characterized by a wide array of symptoms including cognitive decline, parkinsonism and dystonia [1].

Here we show a case of BPAN presenting wearing-OFF phenomena and also peak-dose dyskinesias, as usually observed in Parkinson's disease, particularly in early onset patients. In a previous study motor response to levodopa administration was described in BPAN and the duration of levodopa benefit was reported to be relatively short, with early appearance of motor fluctuations and quickly advancing to disabling dyskinesias [1]. This might be due to the severe dopaminergic depletion in the striatum as assessed by DAT imaging, and the prominent involvement of the substantia nigra by iron accumulation compared to the striatum. Hayflick and colleagues have described levodopa response in 47.8% of BPAN patients, despite the duration of levodopa benefit was short, with early emergence of motor fluctuations determining the discontinuation of drug [1].

Recent reports on BPAN patients have demonstrated widespread tau deposition, indicating that BPAN is a tauopathy [2]. However, our investigation on CSF disclosed a decreased concentration of Aβ1-40 and Aβ1-42, but normal levels of p-tau and t-tau. Studies on Alzheimer's disease (AD) have in fact revealed a significant reduction in Aβ1-40 CSF levels in cognitively normal elderly subjects who subsequently developed AD [3]. By contrast, elevated tau levels occur in individuals who already have cognitive decline, mild cognitive impairment or dementia, and correlate in part with the degree of atrophy [4]. These observations suggest that Aβ aggregation and deposition might be associated with the preclinical phase of AD, whereas changes in CSF tau levels and brain atrophy might represent advanced events. According to that, we might speculate that our findings could reflect an initial phase of the neuropathological mechanisms leading to the frank taupathy described in BPAN in the post-mortem report of Paudel and colleagues [2].

Intriguingly, the accumulation of tau aggregates typically represents a neuropathological feature of patients with atypical parkinsonism usually poorly responsive to levodopa. Moreover, the observation of severe levodopa-induced motor complications is uncommon in taupathies and might

be a disabling feature in BPAN, especially in those patients with prominent iron accumulation in the substantia nigra rather than the striatum.

In addition, our patient developed a sleep disturbance resembling REM behavioral disorder, which is more common in synucleinopathies [5]. Parasomnias are reported in several patients with BPAN, accounting up to 22% of subjects [1] These observations point out that BPAN phenotype may be atypical for taupathies, thus suggesting other potential pathophysiological mechanisms.

The need for a personalized management has started to be regarded as significant factor for delaying and decreasing motor fluctuations on BPAN patient's quality of life. To date, there are no reports on the use of deep brain stimulation to treat parkinsonism in BPAN; nevertheless, the possible worsening of cognitive function in these cases dictates a personalized approach. Further studies addressing dopaminergic response in BPAN might elucidate this peculiar aspect of the disease.

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Legend to figure

Figure. Brain magnetic resonance imaging disclosed iron in the substantia nigra (**A**,**C**) and globus pallidus (**B**,**D**) in axial T2-weighted sequences, with a 'halo' of T1 hyperintense signal in the substantia nigra (**E**). Brain DaT-SCAN showed remarkably reduced bilateral tracer-uptake in the striatum with right putamen/caudate ratio: 0.88, left putamen/caudate ratio: 0.68 (**F**).

Legend to video

Segment 1 (OFF-state): The patient presented with generalized bradykinesia affecting the left limbs more than the right ones, camptocormic attitude of the trunk and dystonic posturing of the left foot. Gait was broad-based and significantly impaired by start and turn hesitation (Unified Parkinson's Disease Rating Scale, part-III: 58/108). *Segment 2 (ON-state):* After one hour from levodopa administration (levodopa+benserazide 100+25 mg), the patient presented with generalized disabling dyskinesias, which significantly impaired standing and walking, and dystonic posturing of the left limbs. Gait was broad-based and severely affected by the dystonic attitude of the left leg (Unified Parkinson's Disease Rating Scale, part-III: 21/108).

Figure(s)

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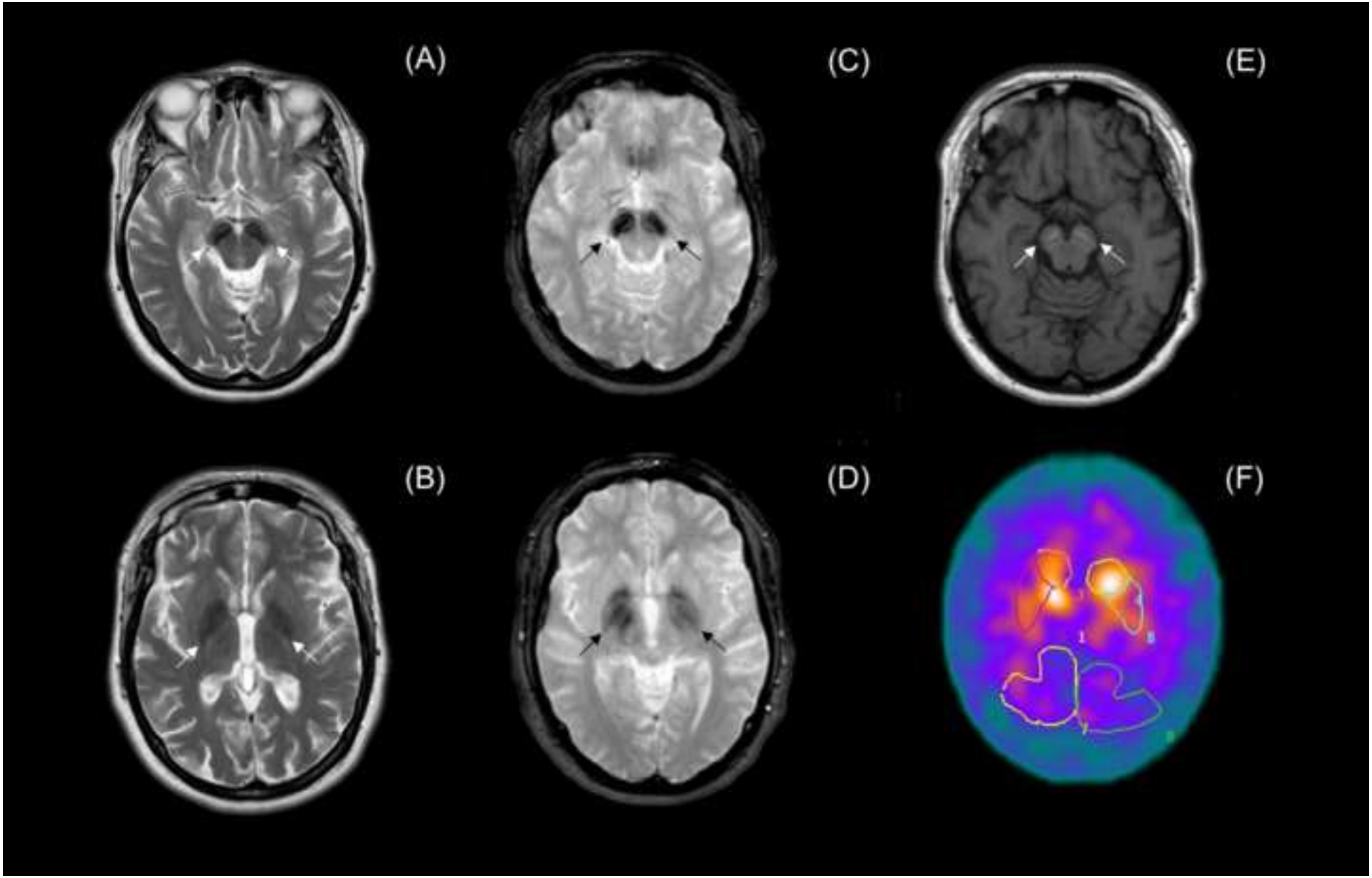

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