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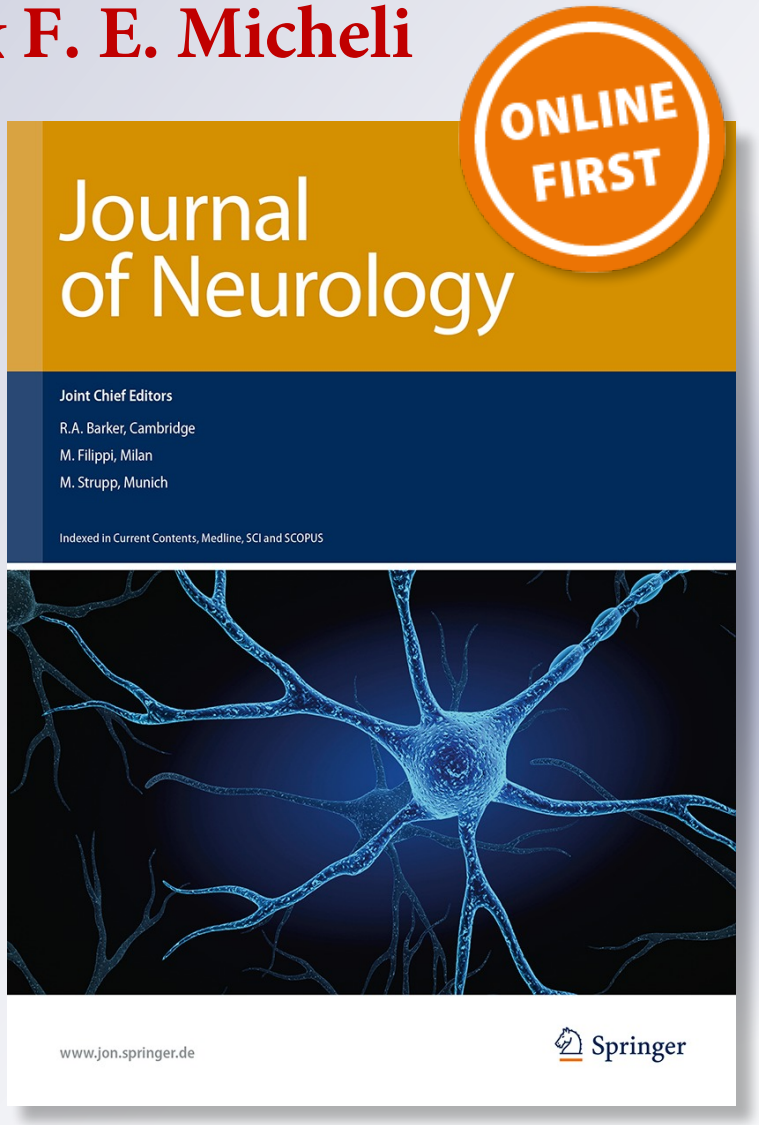

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LETTER TO THE EDITORS

Successful GPi stimulation in genetic Parkinson's disease caused by mosaicism of alpha-synuclein gene duplication: first description

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Dear Sirs,

DBS is an established therapy for advanced PD [1] and has been reported to be efficacious in a few patients with monogenic parkinsonisms such as LRRK2, Parkin, and PINK1 [2–6]. By contrast, knowledge about the outcome of DBS in patients with SNCA mutations is scarce, since only one case has been reported to date [7].

We now report the case of a 26-year-old male with Parkinson's disease due to mosaicism of alpha-synuclein duplication, who has successfully undergone GPi-DBS.

The patient, who has no family history of PD, developed PD at the age of 18. He initially presented dystonic posturing and tremor in his left foot. Within a few months, this had progressed to micrographia, bradykinesia and resting tremor in his upper left limb. He subsequently developed mild autonomic failure, and mild cognitive decline, as well as behavior disorders (rage episodes, panic attacks, and hallucinations). He initially showed good response to dopamine agonists, but after a short period levodopa was needed to obtain satisfactory motor control. He also developed impulse control disorders secondary to treatment with dopamine agonists, resulting in punding behaviors (e.g., disassembling guitars, computers and his car).

FISH was conducted using rhodamine-labeled *SNCA* probes at 4q22.1 (BAC RP11-614o7, 151 kb) and 4q21.3 [BAC-RP11-711j3, 192 kb (control)]. Results indicated few or no rearrangements (i.e., $\leq$4 FISH probe signals in $>$20 % of interphase cells scored) [6] in peripheral leucocytes from the patient, but 43 % of oral mucosa cells showed duplication of *SNCA* gene. No exon dosage rearrangements were detected in *SNCA* or other relevant PD genes using MLPA technique. Mutations in *PINK1*, *PARK2*, and *DJ* were not found and were excluded as causes for the patient's symptoms. Further description of the ancestral origin, genetic tests and immunohistochemical findings of this patient can be found in Perandones et al. [8].

As he rapidly showed disabling motor fluctuations and severe peak-dose dyskinesias refractory to pharmacological strategies, the patient was proposed for DBS. The target chosen was the globus pallidus internus (GPi) based on the dyskinesias that affected his quality of life and the fact that he already presented mild cognitive impairment as demonstrated in the preoperative neuropsychological examination. A quadripolar brain electrode (model 3387, Medtronic) was implanted stereotactically with microregistration technique in each GPi and fixed with the Stimloc system. Magnetic resonance imaging was performed in stereotactic conditions; the images were processed with WinNeus® program to identify coordinates for both GPi. The electrodes were connected to a pulse generator (Activa RC; Medtronic).

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One month after surgery, there was a clinically relevant improvement in motor features and a complete abolition of peak-dose dyskinesias. The patient did not report procedure-related adverse events following GPi-DBS.

In our patient, parkinsonism resembled idiopathic early-onset PD, with the exception of rapid progression, precocious development of motor complications and the early finding of mild cognitive impairment, which are highly unusual. However, such atypical signs have already been described in literature [9].

When the patient was proposed for DBS, 8 years after the beginning of the disease, he met all criteria for implantation protocol in PD with a good response to levodopa complicated by motor fluctuations and severe dyskinesias, with only mild cognitive decline, so GPi-DBS was the established therapy [10].

As far as we know, this is the first report that describes the effect of GPi-DBS in a case of mosaicism of alpha-synuclein gene duplication. The outcome in our patient was comparable with that reported in idiopathic PD [10], with no major adverse events, satisfactory improvement of motor function and reduction of pharmacological treatment.

In conclusion, our case, together with previous reports describing successful DBS in other monogenic parkinsonisms [2–7], strongly supports the concept that surgical indication should be based on the disease phenotype rather than genotype.

Further studies and long-term monitoring are still needed not only to evaluate the potential role of the alpha-synuclein gene mosaicisms in the etiology of early-onset parkinsonisms, but also to confirm the persistence of a successful outcome of DBS in these cases.

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standard The manuscript does not contain clinical studies or patient data.

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