



## Motor and non-motor outcomes of subthalamic deep brain stimulation in a case of juvenile PARK-PINK1



To the Editor,

Deep brain stimulation (DBS) is an established therapy for advanced Parkinson Disease (PD). The widespread application of DBS and the advancement in research on PD genetics have raised interest in understanding whether a differential treatment response in PD patients might be influenced by underlying genetic mutations [1,2]. To date, literature reports mostly on patients with frequent mutations. Although *PINK1* (PTEN-induced putative kinase 1) is the second most common (2–7% of cases) genetic mutation associated with early-onset PD, the outcome of DBS has only been described in two patients with homozygous *PINK-1* mutations so far [3,4]. *PARK-PINK1* is usually considered indistinguishable from sporadic PD, with a good levodopa response and development of motor fluctuations and dyskinesia. A characterizing sign may be the presence of an early-onset lower-limb dystonia [4].

We here describe the case of a patient with homozygous 619C>T-p. (Arg207\*) *PINK-1* mutation, who underwent bilateral subthalamic nucleus (STN)-DBS in our centre and was followed-up for three years (Fig. 1). His medical history was positive for gout, arterial hypertension, paroxysmal atrial fibrillation, and post-traumatic L1-L3 fracture. Family history was characterized by two brothers (out of four) affected by tremor-dominant PD from the age of 48 and 53, with unknown genetic status.

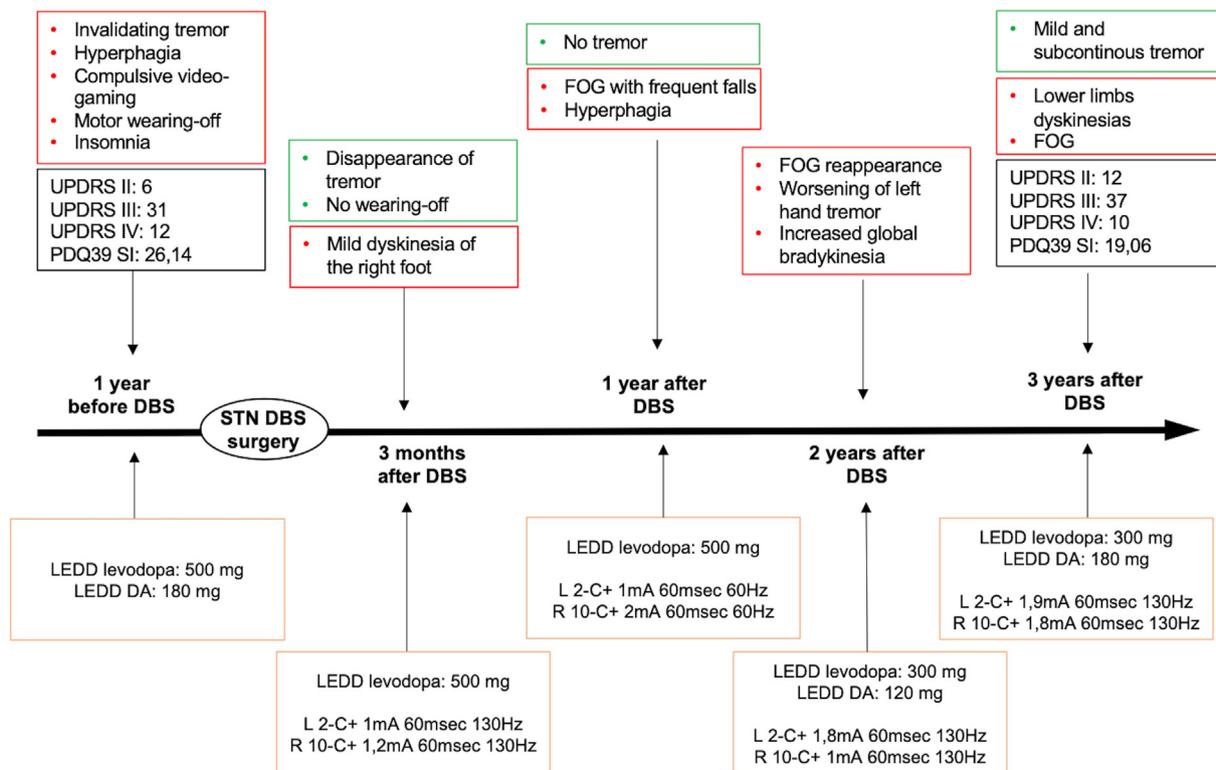
At the age of 38, in 2003, the patient complained rest tremor of the right upper limb and anxiety. In 2004, after the diagnosis of PD, the patient started levodopa with benefit. The [<sup>123</sup>I]FP-CIT SPECT (DaTSCAN) showed bilateral reduction in caudate nucleus and especially in putamen uptake, more remarkable on the left side; cardiac <sup>131</sup>I-MIBG scintigraphy was normal. At the age of 48 the patient started rotigotine 6 mg/day due to the worsening of motor symptoms, but developed impulse control disorder (ICD), characterized by binge eating and compulsive video gaming; an attempt to tapering rotigotine was made, but previous dosage had to be restored due to the worsening of tremor and bradykinesia. Thirteen years after symptoms onset (2016), the patient complained severe motor fluctuations and worsening of motor symptoms; therefore, he was evaluated for DBS. The levodopa challenge test demonstrated a 40% improvement of the Movement Disorders Society Unified Parkinson's Disease Rating Scale part III (Supplementary Table 1); despite a Mini Mental State Examination score of 30/30, the neuropsychological assessment showed a multi-domain (amnestic and executive) mild cognitive impairment (MCI). The patient underwent STN-DBS in 2017. The correct positioning of the electrodes was evaluated by means of post-operative MRI (Supplementary Fig. 1). A marked lesional effect was observed after

surgery, with immediate regression of upper limb tremor and appearance of lower limbs dyskinesias. After DBS activation (bilateral monopolar cathodic stimulation, pulse width 60 us, frequency 130 Hz, amplitude 1.0 mA (left) and 1.2 mA (right)), a marked improvement on motor symptoms and fluctuations was observed; LEDD was tapered (Supplementary Table 1). One year after surgery the patient developed axial and lower limbs dyskinesias and freezing of gait (FOG), with gait and balance impairment. In the attempt of ameliorating axial symptoms, the stimulation frequency was lowered from 130 Hz to 60 Hz, providing an improvement of gait, with only mild worsening of tremor. Two years after surgery, the patient experienced worsening of FOG, bradykinesia, upper limbs tremor, and increased daytime sleepiness; despite improvement of compulsive video-gaming, the patient developed hyperphagia determining a weight gain of 20 kg compared with the presurgical condition. 130 Hz stimulation frequency was restored obtaining an improvement of tremor and bradykinesia, but worsening of gait. At the three-year post-operative follow-up (Supplementary Table 1), the patient complained increased dyskinesias, sub-continuous tremor, and gait impairment with frequent falls, mainly due to FOG. However, motor fluctuations were still relatively controlled, and the patient reported an improvement in quality of life compared to the presurgical condition (Supplementary Table 1). Measures of psychiatric symptoms remained stable and the patient and his caregiver reported good control of ICD.

The influence of genetic mutations on the DBS outcome is of utmost interest to inform prognosis and tailor treatment, also considering that genetic mutations tend to be over-represented in cohorts of DBS patients [5]. Moreover, considering their young age of onset, good levodopa response, and tendency to develop motor complications, PD patients with *PARK-PINK-1* mutations could represent good candidates for DBS.

To date, there are only two published reports of PD patients carriers of homozygous *PARK-PINK-1* mutations who underwent DBS, in one case targeting the STN [3], in the other targeting the Globus Pallidus internus (GPi) [4]. In both cases, the clinical outcome was positive (Supplementary Table 1). Cases of heterozygous *PINK-1* mutations, sometimes in association with other mutations in PD-related genes, have been described [1,2,6,7]; however, it is difficult to understand the influence of these mutations to the clinical picture.

In contrast to other reported cases, our patient developed axial symptoms early after surgery. He was treated with low frequency stimulation to improve FOG and gait; however, after an initially satisfying response, he reported a worsening of cardinal symptoms



**Fig. 1. Timeline of clinical evolution and stimulation settings in the reported case.** Unified Parkinson's Disease Rating Scale (UPDRS); The Parkinson's Disease Questionnaire Single Index (PDQ-39 SI); Deep Brain Stimulation (DBS); Subthalamic Nucleus (STN); Globus Pallidus Internus (GPi); milliampere (mA), microseconds (msec); Hertz (Hz); Levodopa equivalent daily dose (LEDD); Dopamine agonists (DA); Left (L); Right (R); Freezing of gait (FOG).

and a waning effect on FOG, as previously reported [8], requesting restoration of 130 Hz.

Our patient suffered from ICD that, despite the impossibility to withdraw rotigotine, improved significantly after STN-DBS [9]. On the other hand, he gained over 20 kgs in the years after DBS; weight gain has already been reported as a side effect of STN-DBS and can be due to different mechanisms [10]. The non-motor symptoms burden was not clearly influenced by STN-DBS treatment, and the Non-Motor Symptoms Scale (NMSS) total score remained substantially unchanged before and after surgery (Supplementary Table 1).

To our knowledge, this is the longest and most comprehensive follow-up of a PD patient carrier of homozygous *PARK-PINK-1* who underwent STN-DBS. We observed an initial benefit that was followed by worsening of axial symptoms and lower limb involuntary movements. One might argue that the decision of considering STN-DBS in PD patients carriers of *PARK-PINK-1* requires a careful balance between risks and benefits. Nevertheless, our patient reported an overall improvement of quality of life despite the difficult management, which might justify STN-DBS as a potentially useful intervention. Further studies including PD patients carriers of *PARK-PINK-1*, possibly at different clinical stages, are needed to clarify the role of STN-DBS in genetic forms of PD.

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**Ethics approval and patient consent**

The patient provided informed consent on the publication of this case.

**Declaration of competing interest**

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## Appendix A. Supplementary data

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