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G325R *GBA* mutation in Parkinson's disease: Disease course and long-term DBS outcome

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Glucocerebrosidase gene (*GBA*) mutations are implicated in Gaucher's disease (GD) and represent the most common genetic risk factor for the development of Parkinson's disease (PD) [1]. Patients with *GBA* mutations may be younger and have a greater burden of nonmotor symptoms and cognitive impairment than sporadic PD, but on an individual level, the clinical course may be indistinguishable [2]. It has been postulated that genetic variants associated with the most severe forms of GD can be associated with a more aggressive PD course [1,3]. However, only a few among the 130 *GBA* variants linked to PD have been clinically characterized [1].

Studies investigating the role of genetics in deep brain stimulation (DBS) outcome highlighted that carriers of *GBA* mutations may undergo DBS earlier and develop cognitive impairment early after surgery, likely due to a faster disease progression [4,5]. However, given the high number of *GBA* mutations and their high prevalence in both the general PD population and DBS treated patients, it is important to clarify the weight of specific *GBA* variants on the disease natural history and on DBS outcome.

We report here the case of a woman with young-onset PD successfully treated with subthalamic (STN)-DBS presenting the rare heterozygous missense c.1090G > A (G325R; now called G364R). Her family history was negative for neurological and psychiatric disorders, and medical history was unremarkable. At the age of 32, in 1998, the patient developed dystonia of the right upper arm and rigidity of right limbs. In 2001 she received a diagnosis of idiopathic PD and began cabergoline, which was discontinued due to nausea and visual hallucinations and replaced with levodopa with benefit. Constipation and episodic urinary incontinence characterized her nonmotor clinical picture. In 2002 the patient started pramipexole because of worsening of motor symptoms and experienced an episode of major depression resolved in few months with antidepressants (Duloxetine). Five years after the onset of motor symptoms, the patient developed motor and nonmotor fluctuations and dyskinesia. Amantadine and entacapone led to partial improvement and she was referred to our center for considering DBS. In 2007 the levodopa challenge test demonstrated a dramatic improvement (82%) of the Unified Parkinson's Disease Rating Scale (UPDRS) part III and the neuropsychological assessment showed a normal cognitive profile and moderate anxious and depressive symptoms (Supplementary Table 1). The same year the patient underwent bilateral STN-DBS surgery without perioperative complications. After surgery, levodopa equivalent daily dose (LEDD) was tapered from 690 mg to 375 mg and DBS was turned on (monopolar cathodic stimulation: 60 us, 130 Hz, 1.6 V bilaterally) with a marked improvement of motor symptoms, fluctuations, and activities of daily living (Supplementary Table 1 and Fig. 1). In 2009 the patient was admitted to the psychiatric ward for an episode of hypomania, and a bipolar disorder was diagnosed; therapy with valproic acid was initiated with benefit. In subsequent years, both motor and psychiatric symptoms were adequately compensated. Five years after surgery the patient complained of off episodes, dyskinesia, lower limb dystonia which invalidated walking; in that period, episodes of bizarre gait were observed during outpatient visits, with a diagnosis of possible functional movement disorders complicating dyskinesia (Supplementary Video 1). Levodopa, pramipexole, and stimulation amplitude were slightly decreased with poor results; she was therefore hospitalized to review stimulation parameters and therapy obtaining a good symptom control by setting stimulation amplitude at 3.3 V on the left and 3.4 V on the right STN, and reducing LEDD to 400 mg. An attempt to reduce stimulation frequency to 80 Hz was made but not tolerated due to recurring motor fluctuations. Fourteen years after DBS implant motor fluctuations were still well controlled (apart from mild, non-invalidating dyskinesia), cognitive functions were still preserved, and no signs of psychiatric and functional symptoms were present (Supplementary Table 1, Supplementary Video 1).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.brs.2021.08.002

The G325R missense *GBA* variant is rare and has been associated with GD type II [6], causing an acute neuronopathic form of GD which evolves from hepatosplenomegaly and growth arrest to extrapyramidal and cranial nerve involvement [7,8]. To the best of our knowledge, G325R mutation has been reported only in one PD patient [9], and the associated clinical phenotype has never been described.

In contrast to other reported cases of PD linked to *GBA* mutations, our patient did not develop cognitive impairment, REM sleep behavioral disorders, dysphagia and disabling axial symptoms, even after a disease duration of 23 years. She underwent DBS nine years after the motor symptoms onset, which is not substantially different from the time to DBS of sporadic PD. Remarkably, her nonmotor symptoms were characterized by depression,

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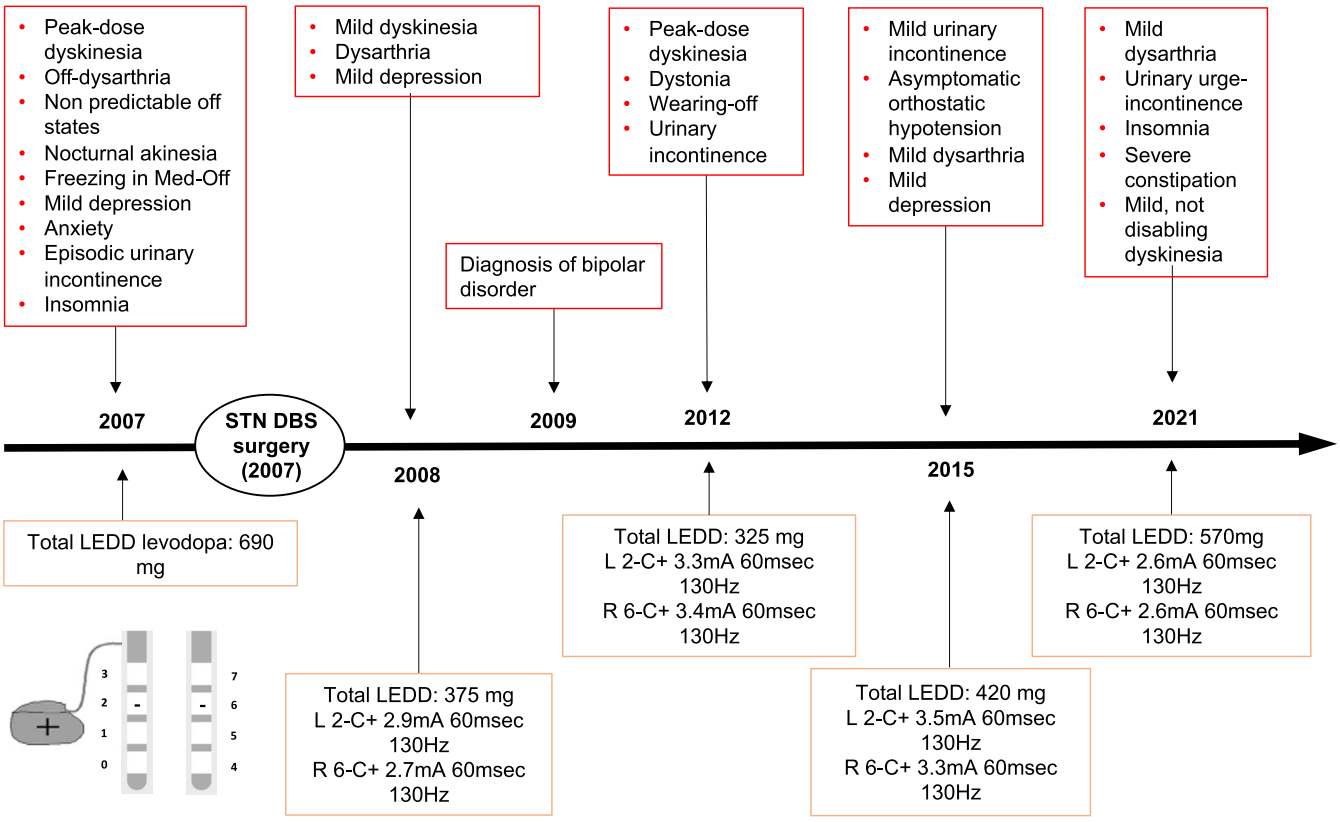

Fig. 1. Disease course and Deep Brain Stimulation outcomeDeep
Brain Stimulation (DBS); Subthalamic Nucleus (STN); milliampere (mA), microseconds (μs); Hertz (Hz); Levodopa equivalent daily dose (LEDD); Left (L); Right (R).

anxiety, urinary dysfunction, and bipolar disorder, but her cognitive and neurobehavioral performances remained stable over time and did not decline after DBS surgery [1,4,10].

Considering that a single patient cannot be representative of the clinical phenotype of this *GBA* variant, we believe that our case can add to the scarce but increasing literature of PD patients with *GBA* mutations treated with DBS, highlighting the important aspect that *GBA* mutations are not necessarily associated with poor DBS outcomes, as previous data seem to indicate [5].

Declarations of interest

None.

Author contributions

Claudia Ledda: Conceptualization, Methodology, Writing – Original Draft, Writing - Review & Editing.

Carlo Alberto Artusi: Conceptualization, Methodology, Writing – Original Draft, Writing - Review & Editing.

Maurizio Zibetti: Conceptualization, Methodology, Writing - Review & Editing, Supervision.

Elisa Montanaro: Conceptualization, Writing - Review & Editing.

Tiziana Martone: Validation, Writing - Review & Editing.

Leonardo Lopiano: Conceptualization, Methodology, Writing - Review & Editing, Supervision.

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Ethical compliance statement

The authors confirm that the approval of an institutional review board was not required for this work. Oral and written informed consent was obtained from the patient for publication of this case.

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.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.08.002.

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