

Don't Disregard Deep Brain Stimulation in Patients with Concomitant Gaucher and Parkinson Disease

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Abstract

Gaucher disease and Parkinson's disease can co-occur, and mutations in the glucocerebrosidase (GBA) gene are considered the most common genetic association with Parkinson's disease. Response to pharmacological and surgical therapies is poorly studied. We present the case of a patient diagnosed with Gaucher disease at 18 years old. At 59 years old right foot dystonia was first noticed. Levodopa was initiated and two years later motor dyskinesias were incapacitating. Although neuropsychological testing showed frontal dysfunction, as the deficit was stable, subthalamic nucleus deep brain stimulation was tried in October 2017. More than one year later the patient remains active and autonomous.

Keywords: Parkinson's disease; neuropsychology; Gaucher disease; GBA gene mutation

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Introduction

Gaucher disease (GD) is the most common lysosomal storage disorder, and it is due to homozygous or compound heterozygous mutations in the glucocerebrosidase (GBA) gene (O'Regan, deSouza, Balestrino, & Schapira, 2017), coding the enzyme β -glucocerebrosidase (Rodriguez-Porcel, Espay, & Carecchio, 2017). It is a multisystem disease, traditionally classified into three clinical subtypes. Concomitant Gaucher and Parkinson's disease (PD) is rare, and literature on PD-related phenotype, response to pharmacological therapy, and deep brain stimulation (DBS) is scarce. Despite the rarity of the association, mutations in the GBA gene have been coined as one of the most common genetic associations with PD (Balestrino & Schapira, 2018), although the underlying mechanism is still

poorly understood (O'Regan et al., 2017). Furthermore, it was found that even heterozygous carrier status is associated with PD, and is, at present, the most frequent known risk factor for PD (Goker-Alpan et al., 2004). It is estimated that up to 30% of GBA mutation carriers will progress to develop PD by the age of 80 (Anheim et al., 2012). There seems to be a "dose response," dependent on GBA burden (Thaler et al., 2018).

GD usually precedes the onset of PD (Collins et al., 2018). A clinical series of 19 patients with concomitant Gaucher and PD found an earlier mean age of onset of PD, shorter disease duration, and poorer response to levodopa (Lopez et al., 2016). Collins et al. (2018) found that motor symptoms were typical and indistinguishable from idiopathic PD. There are conflicting data regarding the rate of

cognitive decline and neuropsychiatric features, and a recent study did not find significant differences between patients with idiopathic PD and those with GD plus PD (Thaler et al., 2018). Evidence on motor response to DBS in PD patients with Gaucher disease is scarce, and long-term studies evaluating cognitive changes after DBS are lacking.

Case Report/Case Presentation

We present the case of a 63-year-old female diagnosed with GD at 18 years of age, under enzyme replacement therapy with imiglucerase. She had a splenectomy at 24 years of age and had no further systemic complications. Her family history was relevant for 2 of 11 siblings with GD.

In 2012, at 59 years of age, a rest tremor of the right hand was first noticed along with right foot dystonia. Levodopa was tried with a favorable response. After 2014, motor fluctuations and peak dose dyskinesias rapidly became incapacitating. Amantadine and rotigotine were tried, but side effects were intolerable. The patient was referred to our clinic in 2016 to assess the eligibility for DBS. She was under levodopa/carbidopa 25/100 every 3 hours.

The patient was extensively investigated, including with brain CT scan and MRI, both unrevealing. *DaTscan* (with Ioflupane I 123 Injection) showed a markedly reduced uptake in the striatum (left more than right).

At our center, we performed an acute levodopa challenge test. Motor assessment, using the motor (Part III) of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), before (59) and 1 hour after drug administration (35), was documented. Psychiatric evaluation deemed the patient a suitable candidate for surgery. On the other hand, neuropsychological tests at first showed a frontal/subcortical dysfunction associated with a probable comprise of other cortical regions and the patient was found unfit for subthalamic nucleus (STN) DBS by the neuropsychologists. Six months later, a repeated evaluation showed a slight improvement, attributable to a less noticeable emotional lability, and the patient underwent surgery (STN DBS) on October 2017.

At present, 1.5 years after DBS, the patient remains without levodopa, managed solely with the stimulation (ranges of stimulation: Frequency: 150–170 Hz, because tremor was the predominant symptom; Pulse width: 60–90 μ s; Voltage; 1.5–3.0 V). At last follow-up, in the motor assessment in best ON

(Stimulation ON), using Part III of the UPDRS, the patient scored 19. Nonmotor assessment was not performed. Neuropsychological testing one year after surgery showed stable deficits. Disturbing visual hallucinations were reported and are being managed with clozapine, sertraline, and rivastigmine. The patient remains active, partially autonomous, and the major complaint now is language dysfunction, namely aphasia, not attributable to side effects of DBS.

Discussion/Conclusion

There are two approved therapies for patients with GD: enzyme replacement therapy and substrate reduction therapy. Neither is an effective treatment for neurological symptoms, since they don't cross the blood brain barrier (Balestrino & Schapira, 2018). There is no evidence that any of the used treatments reduces the risk of Parkinsonism (Chetrit et al., 2013; Elstein, Alcalay, & Zimran, 2015), and these patients should be treated similarly to those with PD without GD (Elstein et al., 2015).

We report a patient with GD and PD who underwent DBS. We found two other cases amongst a large Israeli cohort (Chetrit et al., 2013). They were considered candidates owing to levodopa-induced dyskinesias. Both patients reported dramatic and sustainable symptomatic improvement. On the other hand, Lythe et al. (2017) reported that patients with GD who had DBS had more severe cognitive impairment compared to PD patients with GBA mutations.

Our aim was to shed light on a group of patients that may benefit from DBS. The problem found by the functional disorders group rested on the cognitive dysfunction found in this patient. At the moment, there is some debate about the acceptable degree of cognitive impairment previous to DBS. The fact that cognitive decline is a known adverse effect of STN DBS further increased our uncertainties. We opted to repeat the neurophysiological evaluation, and there the deficits were stable. Ergo, we decided to follow through with the surgical treatment achieving a positive result (using the MDS UPDRS scale), and according to the patient and her family members. The target used was the STN; however, the GPi could have been a good option, because it may have fewer cumbersome effects in cognition. Our case illustrates a good motor and stable cognitive outcome in patients with concomitant PD and GD submitted to STN DBS.

Author Disclosure

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