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Letters to the Editor Related to Published Articles

Unilateral Pallidotomy in a Patient with Parkinsonism and G2019S *LRRK2* Mutation

We read with great interest the study by Schupbach et al.[1] describing the motor effects of high-frequency stimulation of the subthalamic nucleus (STN) in patients with parkinsonism because of leucine-rich repeat kinase 2 (LRRK2) mutations. The authors presented the outcome of 9 patients with heterozygous LRRK2 mutations out of 69 genetically tested Parkinson's disease (PD) patients operated on for bilateral STN stimulation. Clinical response was similar in both groups; therefore, patients with LRRK2 mutations should be considered as good candidates for this type of intervention.

Although interventions using deep brain stimulation (DBS) have proven to be more efficacious and safe than stereotactic ablative surgery in PD,[2] the latter form of treatment continues to be performed routinely in countries where DBS is not widely available or affordable. We had the opportunity to follow a PD patient who carried a heterozygous G2019S *LRRK2* mutation treated with unilateral pallidotomy. The patient is now 50 years old and presented with an apparently sporadic form of PD at the age of 39 years. Her first symptoms were right hand and foot resting tremor, and right-sided bradykinesia and rigidity. As she could not tolerate even low doses of dopamine agonists (pramipexol and bromocriptine) due to GI side effects, selegiline monotherapy was used during the first year and then L-dopa was started. On follow-up after 3 years, bilateral parkinsonism was noted. After 5 years from onset the patient was taking 800 mg of L-dopa a day divided in four doses, but experienced significant disability caused by peak-dose dyskinesias and motor fluctuations (wearing-off). Amantadine 100 mg tid was added with transient reduction of motor complications. After a few months, the patient returned for a follow up complaining of visual hallucinations with good insight, lower limb edema, and livedo reticularis. As amantadine was withdrawn, dyskinesias on the right side of the body became intolerable leading to dependence for activities of daily living (ADLs). Eventually, a left pallidotomy was recommended. Preoperative assessment included UPDRS part II (OFF) score 25, III (OFF) score 36 and IV items 32–34 (ON) score 5. CT scan was used to determine the position of the target structure. The target coordinates for pallidotomy were 2 mm anterior to the midcommissural point, 5 mm below the intercommissural line, and 22 mm lateral to the midplane of the third ventricle. A macroelectrode was used for test stimulation over a 10 mm distance for each trajectory to identify the optimal target. The final target location was determined in the position where rigidity and bradykinesia improved with the lowest current intensity of high frequency stimulation (100 μs and 130 Hz) and where the fewest side effects occurred with high and low frequency stimulation (maximum 5 V, 100 μs, and 130 Hz and 2 Hz). Radiofrequency thermolesions (60–75°C for 60 seconds) were made in 2 mm steps with the same macroelectrode. Postoperative assessment at 2 weeks showed significant improvements in OFF ADL (16) and motor scores (24) as well as in dyskinesias (score 1 for item 32 and 0 for the remaining). Six months after surgery, scores remained improved compared with preoperative function. Adverse effects included mild and transient confusion in the immediate postoperative period, worsening of salivation, and postural instability (UPDRS item no. 30: 2, no history of falls). On a recent follow-up, the patient consented to participate in an ongoing genetic study, and a mutation screening of the *LRRK2* gene was performed with the identification of a heterozygous G2019S *LRRK2* mutation.

Most cases of parkinsonism with G2019S *LRRK2* mutation described in the literature show a clinical presentation very similar to that of idiopathic PD, including good L-dopa response.[3] As L-dopa responsiveness is one of the best predictors for outcome after STN DBS for PD,[4] the results of the study by Schupbach et al.[1] are not unexpected. To our knowledge, the case described here is the first report of patient with parkinsonism and a documented LRRK2 mutation treated successfully with ablative pallidal surgery. Although a single case report limits extrapolations to a general conclusion, our results were considered to be similar to those of non-genetically linked PD patients routinely operated on in our service. We consider that this type of surgery remains an option when high frequency stimulation is not available.

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References

1. Schupbach M, Lohmann E, Anheim M, et al. Subthalamic nucleus stimulation is efficacious in patients with Parkinsonism and LRRK2 mutations. Mov Disord 2007;22:119–122.
2. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349:1925–1934.
3. Khan NL, Jain S, Lynch JM, et al. Mutations in the gene LRRK2 encoding dardarin (PARK8) cause familial Parkinson's disease:

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clinical, pathological, olfactory and functional imaging and genetic data. Brain 2005;128:2786–2796.
4. Welter ML, Houeto JL, Tezenas du Montcel S, et al. Clinical predictive factors of subthalamic stimulation in Parkinson's disease. Brain 2002;125:575–583.

Reply: Unilateral Pallidotomy in a Patient with Parkinsonism and G2019S LRRK2 Mutation

We thank Dr. Munhoz et al. for their letter commenting on our article on subthalamic nucleus stimulation in patients with Parkinson's disease (PD) and the G2019S mutation in the LRRK2 gene.[1]

They report an interesting case of a patient, with apparently sporadic and typical PD, who was found to be a heterozygous carrier of the G2019S *LRRK2* mutation and whose symptoms and levodopa-induced motor complications improved after left sided pallidotomy.

LRRK2 gene mutations are usually associated with typical parkinsonism. Nevertheless, atypical forms have been reported.[2] Therefore, the indication for deep brain stimulation (DBS) or lesion therapy critically depends on published standard inclusion criteria,[3] independent of the genotype. As we stated in our paper, only PD patients with LRRK2 mutations who fulfill these inclusion criteria for STN stimulation are good candidates for this treatment.[1]

As Munhoz et al. wrote, DBS is viewed to be safer and more efficacious than lesion therapy. In spite of the absence of adequately powered controlled prospective studies, most centers prefer DBS over pallidotomy. However, if DBS is not available, pallidotomy remains a valid therapeutic option.

The relevance of LRRK2 mutations for the outcome of DBS (or pallidotomy) remains to be further investigated.

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References

1. Schüpbach M, Lohmann E, Anheim M, et al. Subthalamic nucleus stimulation is efficacious in patients with parkinsonism and LRRK2 mutations. Mov Disord 2007;1:119–122.
2. Gasser T. Molecular genetic findings in LRRK2 American, Canadian and German families. J Neural Transm 2006Suppl;70:231–234.
3. Welter ML, Houeto JL, Tezenas du Montcel S, et al. Clinical predictive factors of subthalamic stimulation in Parkinson's disease. Brain 2002;125:575–583.

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