Early View

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Deep Brain Stimulation in Patients with Mutations in Parkinson's Disease-Related Genes

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In the era of precision medicine - an effort to identify which approaches will be effective for which group of patients based on genetic, environmental and lifestyle factors[1] - the question whether genetic background should guide specific therapeutic plans in patients with mutations in Parkinson's Disease (PD)-related genes has gained increased relevance.

In this context, we systematically reviewed studies that have evaluated deep brain stimulation (DBS) motor outcome, non-motor symptoms and adverse events in patients with mutations in PD-related genes. Twenty-five studies (135 patients) with available objective motor outcomes were included in this review. To synthetize this data, we defined mean UPDRS III change of 50% or more as marked response, mean UPDRS III change of 30 to 50% as satisfactory response and less than 30% change as unsatisfactory response. Because of the variable postoperative follow-up intervals adopted by different studies, we defined shorter follow-up as mean follow-up less than two years, intermediate follow-up as mean follow-up between two and six years; and longer-term follow-up as mean follow-up of more than six years.

Parkin (PRKN), LRRK2 and GBA were the most frequent mutations in this population. At shorter-term, most patients with PRKN, LRRK2 (except for R144G) and GBA mutation had marked or satisfactory response to STN-DBS; and the improvement seen in the PRKN group was similar when we excluded the single heterozygous PRKN carriers. At the intermediate follow-up, although most PRKN homozygous/compound heterozygous patients and LRRK2 patients had marked or satisfactory responses after STN-DBS; in GBA patients the motor outcome varied equally among marked, satisfactory, and unsatisfactory responses. Longer-term follow-up was rarely reported. As the number of patients varied widely among groups, we emphasize these are all preliminary and exploratory findings. Unfortunately, data on GPi-DBS were scarce and precluded conclusions regarding target selection based on genetic status.

In regards to non-motor symptoms, non-systematic reporting and small sample size limited interpretation of the results. Despite these, worsening of cognition was a consistent finding in GBA patients. However, it is crucial to highlight that none of the studies describing GBA-DBS patients compared the cognitive outcome with GBA-PD patients not subjected to surgery. Higher progression to mild cognitive impairment and dementia has been shown in PD patients with GBA mutations at baseline [2, 3], and it is still unclear whether STN-DBS inputs an additional risk and if GPi would be a safer target in these patients.

In conclusion, our study showed that DBS results in positive outcome at shorter-term in patients with PRKN, GBA and LRRK2 (non-R144G) mutations. Despite limitations regarding small sample size, it is possible that patients carrying GBA mutations may be associated with higher frequency of cognitive and other non-motor symptoms after surgery. Longer and larger cohort's follow-up, with broader non-motor symptoms evaluations, will be necessary to better customize the DBS therapy in this population.

References

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