Intolerance to dopaminergic medication and deep brain stimulation: A report of 3 cases☆

Intolerancia a la medicación dopaminérgica y estimulación cerebral profunda, a propósito de 3 casos

Dear Editor:

Levodopa continues to be the most effective pharmacological treatment for Parkinson's disease (PD).[1] In fact, diagnosis of PD is based on patient response to dopaminergic treatment; lack of response constitutes a warning sign for atypical parkinsonism.[2] Furthermore, response to levodopa constitutes the best predictor of response to deep brain stimulation (DBS). Patients with high-quality ''on'' states present better and more sustained response to DBS.[3]

Some patients with PD are intolerant to levodopa, particularly in early stages of treatment. This is usually solved with slow, progressive dose adjustment and the use of peripherally-acting prokinetics, such as domperidone.

We present the cases of 3 women with PD treated with bilateral subthalamic DBS despite intolerance to dopaminergic treatment (different formulations of levodopa and oral or transdermal dopaminergic agonists) and such other antiparkinsonian drugs as rasagiline. Intolerance to the drug prevented us from performing the levodopa challenge test in all 3 cases. While patient 3 partially tolerated the apomorphine test, none of the patients tolerated treatment with continuous infusion of apomorphine.

In all cases, DBS achieved marked improvements in parkinsonian symptoms, especially in patients 1 and 3, who also presented severe resting tremor in the limbs. Our patients' clinical characteristics and progression data are summarised in Table 1. None of the patients presented any immediate complications of surgery or adverse reactions to DBS.

DBS was the only viable treatment option in our patients. Despite potential doubts arising due to the lack of response to dopaminergic treatment, diagnosis of PD was clear in all 3 patients. All 3 met the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria; according to the more recent criteria established by Postuma et al.,[2] a diagnosis of clinically probable PD could be established in all cases. Presence of parkinsonian tremor and the lack of signs compatible with postsynaptic parkinsonism after several years of progression did not suggest any alternative diagnosis. During the initial stages of diagnosis, patients 2 and 3 underwent DaTSCAN studies, which revealed bilateral, asymmetric reduced tracer uptake. Strictly speaking, none of our patients was in an advanced stage of the disease since they did not present fluctuations or complications associated with treatment, nor did they present axial or cognitive symptoms, which may have represented a contraindication for DBS.

Lack of response to dopaminergic treatment is not only a warning sign but also an exclusion criterion for DBS.[4] Furthermore, lack of response prevents us from predicting the clinical benefits of DBS, since the purpose of the treatment is to achieve the best and most stable pharmacological ''on'' state.

The interest of cases 1 and 2 lies in the fact that both patients underwent surgery for DBS despite never having shown response to dopaminergic agents, either as treatment or in a responsiveness test.[5] Although lack of response constitutes a formal exclusion criterion, we should bear in mind that it represents intolerance to a particular medication, rather than lack of an actual response. We believe that DBS should not be ruled out in these patients without careful analysis of other relevant factors since this treatment is the only option that may achieve prolonged relief of their symptoms. In the case of patient 3, 4 years have passed since she underwent surgery for DBS electrode placement, and she continues to display an excellent response (UPDRS-III: 8; Hoehn and Yahr: 2).

Table 1 Patient characteristics and progression after deep brain stimulation.

Patient	Age/sex	Disease progression (years)	UPDRS-III/H&Y before DBS	UPDRS-III LD/APO test	UPDRS-III 1 month DBS	UPDRS-III 6 months DBS	UPDRS-III/H&Y 12 months DBS
1	72/W	7	43/4	Not tolerated	12	8	8/2
2	66/W	12	39/3	Not tolerated	19	12	10/2
3	64/W	8	46/4	APO 2 mg; 26	15	8	4/1

APO: apomorphine; DBS: deep brain stimulation; H&Y: Hoehn and Yahr scale; LD: levodopa; UPDRS: Unified Parkinson's Disease Rating Scale; W: woman.

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Encephalopathy and adrenal insufficiency secondary to anti-glutamic acid decarboxylase antibodies☆

Encefalopatía e insuficiencia suprarrenal secundaria a anticuerpos antiácido glutamil decarboxilasa

Dear Editor:

Although autoimmune encephalopathies are frequently described,[1] encephalopathies associated with autoimmune polyglandular syndromes with antibodies targeting glutamic acid decarboxylase (anti-GAD) are much rarer.[2] We present a case of encephalopathy associated with anti-GAD antibodies and adrenal insufficiency manifesting with akinetic mutism and non-convulsive status epilepticus.

Our patient was an 82-year-old woman with history of hypothyroidism. She was admitted due to a one-month history of unsteady gait, hyporexia, and weight loss. The week before admission, she presented disorientation and bradypsychia. Laboratory analysis detected hyponatraemia (118 mEq/L). Despite slow correction of sodium levels (123 mEq/L at 24 hours), she presented hallucinations, confusion, and finally severe akinetic mutism within hours. She also presented oropharyngeal candidiasis.

Contrast brain MRI and head CT scans showed no relevant alterations. A CSF analysis yielded no abnormal results. Subsequent follow-up blood analyses revealed no significant improvement in sodium levels, with concentrations ranging from 125 to 128 mEq/L despite restriction of water intake and administration of hypertonic saline. Osmolality was low in the serum (255 mOsm/kg) and normal in urine (550 mOsm/kg). Chest, abdomen, and pelvis CT and PET/CT scans revealed no abnormalities. EEG revealed non-convulsive status epilepticus. We started treatment with lacosamide and subsequently intravenous valproate, which improved EEG activity; akinetic mutism persisted, however. Suspecting autoimmune encephalopathy, we requested an immunological study including tests for antibodies associated with the disease, and started empirical treatment with intravenous methylprednisolone 1 g/day for 5 days. The patient showed a partial improvement, with fluctuation of the symptoms, and we subsequently started treatment with intravenous immunoglobulins dosed at 0.4 g/kg/day for 5 days, achieving significant improvements in her clinical status. Adrenal insufficiency, hypoglycaemia, and hyponatraemia improved after administration of hydrocortisone. The immunological study revealed high anti-GAD antibody titres (119; normal range, <10); vitamin B_{12} deficiency (192 ng/L) and presence of anti—gastric parietal cell antibodies (titre of 1/80) were also detected. Gastroscopy revealed atrophic gastritis. Treatment led to clinical, electrophysiological, and EEG improvements; the patient continued to present disorientation and slightly decreased speech fluency. We administered 2 additional cycles of intravenous immunoglobulins; the patient has presented no further relapses after 6 months of follow-up.

Glutamic acid decarboxylase is expressed in the pancreatic islets and the central nervous system.[3] One of its functions is to convert glutamate into gamma-aminobutyric acid (GABA). The neurotransmitter GABA has an inhibitory function in the central nervous system. Anti-GAD antibodies act mainly on the GAD65 isoform, which is directly involved in neurotransmission, inhibiting the conversion of gluta-

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