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Deep brain stimulation in status dystonicus caused by anti-NMDA receptor encephalitis

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Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is the most common type of autoimmune encephalitis, mostly affecting young patients. In children, movement disorders are the predominant manifestation of anti-NMDA receptor encephalitis including chorea, stereotypies, tremor, myoclonus and generalized dystonia [1]. Herein we report a case of anti-NMDA receptor encephalitis presenting with status dystonicus (SD) resistant to immunosuppressive therapies who responded well to bilateral Globus Pallidus Internus (GPi) deep brain stimulation (DBS).

1. Case report

An 11-year-old boy was referred to our hospital due to subacute onset of behavioral changes, school performance deterioration and abnormal limb movements.

Patient's mother had a normal pregnancy and birth without history of neonatal jaundice or asphyxia. His motor milestones were completely normal and he had a good performance at school before this presentation. Symptoms started one month earlier following a nonspecific upper respiratory tract infection. Abnormal movements also resulted in imbalance and gait disturbance. On admission he had choreo-dystonic movements of limbs and perioral area, which gradually increased in severity and made speaking, sitting and standing impossible. Dystonia progressed in few days and he was admitted to the ICU with a diagnosis of 'monophasic SD' [2], where he also manifested several episodes of generalized tonic-clonic seizures, controlled with anti-epileptic medications. Initial investigations for Sydenham's chorea, Wilson's disease, collagen-vascular diseases and infectious encephalitis were negative. Serum ammonia, lactate and other metabolic markers were normal. Brain MRI was normal. EEG showed diffuse slowing without delta brush waves. Since autoimmune encephalitis was a possible diagnosis, patient received intravenous immunoglobulin (IVIG) followed by methylprednisolone pulse. Poor concentration, seizure and abnormal behavior responded to initial treatments but abnormal movements (dystonia) responded poorly.

A diagnosis of anti-NMDA receptor encephalitis was confirmed with CSF analysis (IgG against the GluN1 subunit of NMDA receptor). Chest CT-scan, abdominal MRI and testicular sonography excluded an associated malignancy (repeated twice over 18 months).

In spite of the initial response to treatment, dystonia progressed in severity and was resistant to additional immunomodulating (including further steroid pulse, IVIG, plasma exchange and rituximab) and symptomatic treatments (trihexyphenidyl 40 mg, diazepam 30 mg and baclofen 20 mg per day).

A repeated brain MRI nine months after disease onset showed mild to moderate supratentorial atrophy. A second CSF analysis was negative for anti NMDA, AMPA1, AMPA2, GABA-B, CASPAR2 and LGI1 antibodies.

Due to the refractory SD (Video 1), the patient eventually underwent bilateral GPi DBS, which induced a delayed improvement especially after frequency and pulse width were increased (Video 2). Rituximab was also continued for four months, one dose per month. At the last visit, 18 months after disease onset and 9 months after DBS, the patient was able to speak and swallow without difficulty and stand and walk a few steps with braces and unilateral aid (Video 3). The movement and disability scores on Burke-Fahn-Marsden Dystonia Rating Scale dropped form 98 and 30 before DBS to 42 and 17 respectively after DBS. The latest stimulation settings were bilateral monopolar configuration with amplitude of 2.1 V, pulse-width of 90 microseconds and frequency of 180 Hz (more details are presented on Fig. 1).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.07.023

2. Discussion

Movement disorders are an extremely common feature of anti-NMDA receptor encephalitis especially in children, in whom these are prominently hyperkinetic movements of limbs and orofacial area [1].

Anti-NMDA receptor encephalitis and other autoimmune encephalitis should be included among the etiologies of SD due to their clinical course, topography, phenomenology and need for specific therapeutic intervention [2]. In the most recent literature review of 373 cases of pediatric anti-NMDA receptor encephalitis, the outcome was favorable in 50.1% (complete improvement with minor deficits) whereas 46.7% had incomplete recovery and 3.2% resulted in major deficits or death [3]. Due to the poor response to immunotherapies in our patient, DBS was considered as the last therapeutic resort. GPi DBS is an effective treatment for dystonia with better results in isolated

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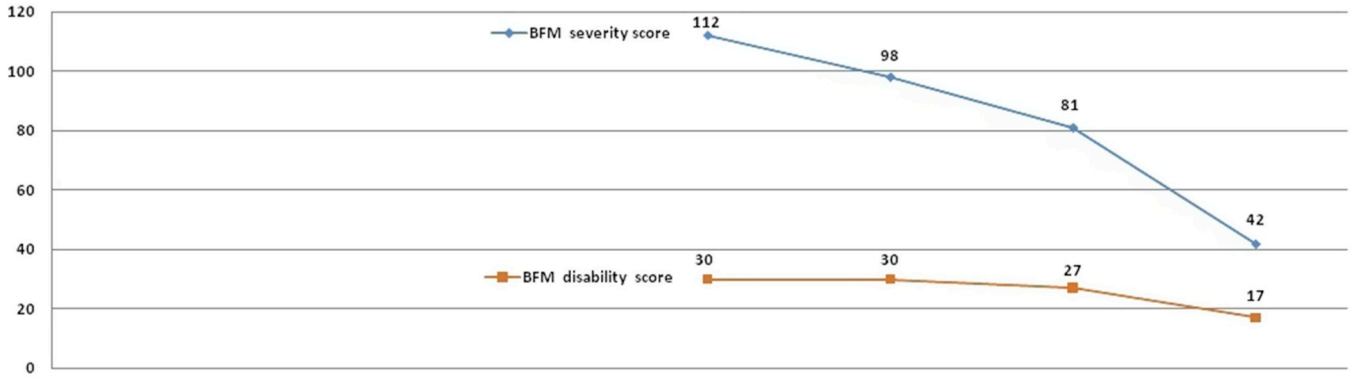

Disease time course	0	Week 3	Month 2	Month 6	Month 12	Month 18
Symptoms	Upper respiratory tract infection, nausea, vomiting, epigastric pain	Behavioral changes, poor concentration, irritability, dyskinesia, dysarthria and dysphagia, seizure episodes	Irritability and generalized dystonia	Generalized disabling dystonia	Generalized dystonia	Generalized dystonia, partially improved
Treatments	Nothing	ICU admission, IVIG(0.4gr/kg per day for 5 days), methylprednisolone (20mg/kg/day) for 5 days), anti-epileptic medications (Phenytoin, Sodium valproate and levethiracetam) trihexyphenidyl, baclofen and diazepam	Second course of Methylprednisolone (20mg/kg/day) for 5 consecutive days) followed by Rituximab (375mg/m^2/course), two courses separated by 1 month	Bilateral GPi DBS trihexyphenidyl, tetrabenazine, diazepam and baclofen	DBS trihexyphenidyl, tetrabenazine, diazepam and baclofen	DBS trihexyphenidyl, tetrabenazine, diazepam and baclofen
DBS parameters	-	-	-	Monopolar stimulation on both sides, amplitude: 2 volts, pulse width: 60 microseconds, frequency: 130 Hertz	Monopolar stimulation on both sides, amplitude: 4.1 volts, pulse width: 60 microseconds, frequency: 130 Hertz	Monopolar stimulation on both sides, amplitude: 2.1 volts, pulse width: 90 microseconds, frequency: 180 Hertz

Fig. 1. This figure shows the time course of the disease, the treatments the patient received and the response to treatments according to BFM severity and disability scores. Stimulation parameters are also presented.

dystonias and lesser efficacy in acquired ones [4]. There are few case reports of DBS as a rescue treatment for patients with SD. Ben-Haim et al. reported 28 cases of SD of which 26 patients recovered from dystonic storm with DBS or neuro-ablative surgeries (23 out of 28 patients underwent DBS) [4]. There is only one case report of DBS in autoimmune encephalitis, an adult case of Rasmussen encephalitis with severe refractory unilateral dystonia that responded well to unilateral GPi DBS [5]. Our experience shows that bilateral GPi DBS might be considered as a rescue strategy for movement disorders caused by anti-NMDA receptor encephalitis refractory to immunosuppressive treatments.

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