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Clinical letter

Deep brain stimulation for the management of seizures in MECP2 duplication syndrome

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What this paper adds

- This case report is the first to describe the use of deep brain stimulation in a patient with MECP2 duplication syndrome and intractable seizures.
- We discuss the potential role of DBS in this population.

Chromosomal duplication at the Xq28 region including the MECP2 gene (MECP2 duplication syndrome) is one of the most common genomic rearrangements identified in neurodevelopmentally delayed males. The main clinical features include infantile hypotonia, mild dysmorphic features, cognitive delay, absent speech, recurrent infections, progressive spasticity and autism. More than 50% of affected individuals develop epilepsy with a high reported rate of drug resistant seizures. Up to 40% of patients die before the age of 25 years with respiratory infections being a frequent cause of death.[1]

Here we describe the long-term evolution of a 35 year-old patient with MECP2 duplication syndrome who at the age of 20 years received deep brain stimulation (DBS) to the anterior nucleus (AN) of the thalamus for the management of pharmacoresistant seizures. Informed consent was obtained from the patient's caregiver to publish this report.

1. Case report

Developmental delay was first observed at 9 months of age. Independent walking was attained at 3 years. Speech was late and he was never able to speak in full sentences. At 10-years-old, the patient had some manual dexterity, was able to play soccer and horseback ride. Speech and motor abilities were lost after the onset of seizures at the age of 14. One year later he was not able to read, count, or dress himself. It is not clear when the patient lost the ability to walk as he was forced to use a wheelchair at all times due to atonic seizures starting at the age of 15. Over his life he has had multiple aspiration pneumonias, each time leading to ICU admission and assisted ventilation. At 28-years-old a G-tube was inserted due to recurrent aspiration pneumonias. Currently, at 35-years-old the patient is wheelchair bound with spastic quadriparesis worse in the legs. He has severe cognitive delay, does not talk nor does he respond to simple commands or make eye contact. He shows frequent stereotypic movements characterized by head bouncing down and to the side.

Seizure history: complex partial seizures (CPS) started at the age of 14 years. Atonic seizures began one year later. He subsequently developed secondarily generalized tonic clonic (2ly GTC) seizures, atypical absence, tonic and eating-reflex seizures (head drop associated with generalized epileptic discharges). His seizures could not be controlled on different combinations of the following drugs: valproate, phenytoin, clobazam, felbamate, carbamazepine, lamotrigine, ethosuximide, vigabatrin, gabapentin and topiramate.

Admission to the Epilepsy Monitoring Unit with continuous video-EEG (expanded 10–20 international system with zygomatic and subtemporal electrodes) revealed abnormally slow background activity. Interictal epileptiform discharges (IEDs): 2 Hz-spike-and-slow-waves with generalized distribution and bilateral synchrony, as well as multifocal independent spike foci (Fig. 1). Atonic seizures (Fig. 2) and 2ly GTC seizures without clear onset localization were recorded. MRI showed mild hyperintensity in the white matter around the ventricular trigones.

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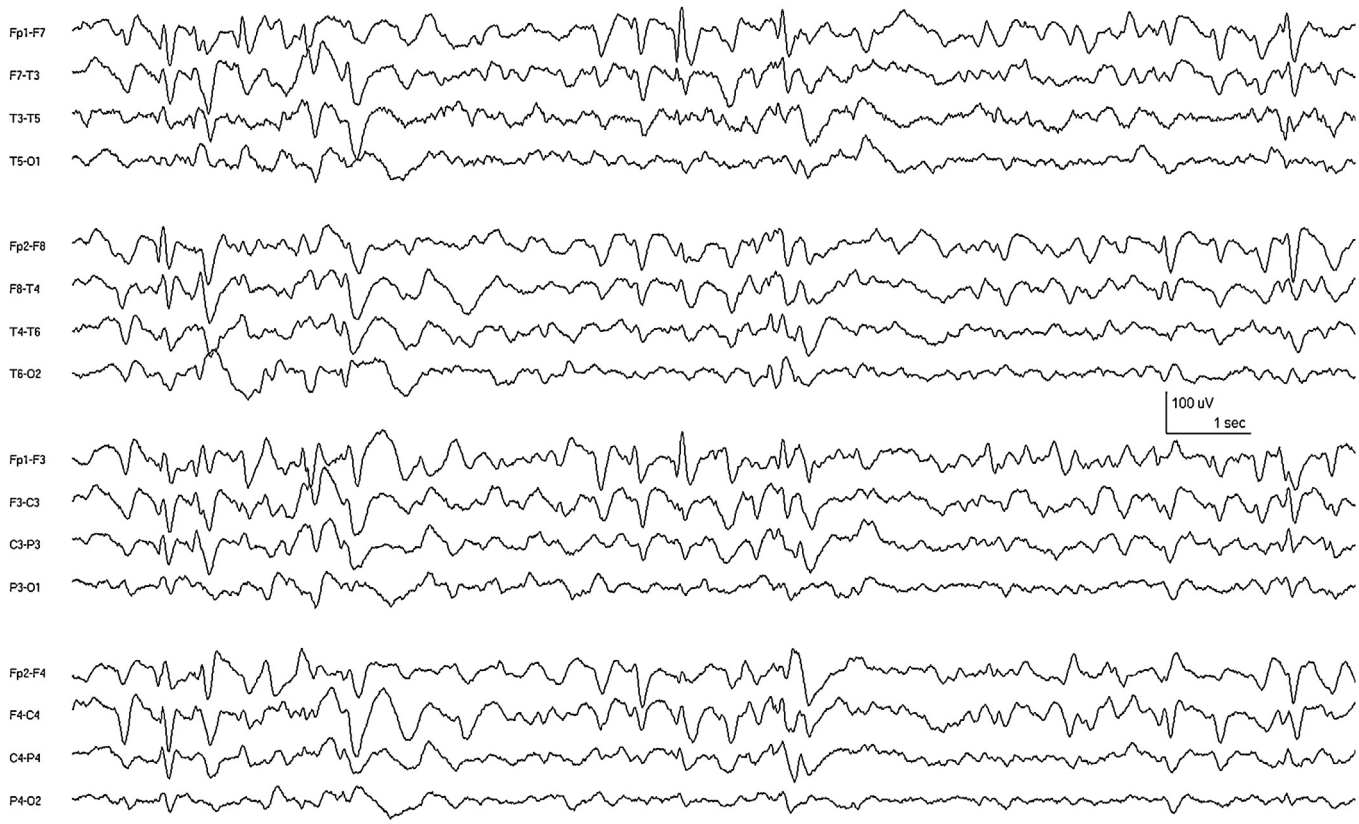

Fig. 1. Interictal EEG showing generalized, frontally predominant slow spike and wave discharges. Bipolar anterior–posterior longitudinal montage. Time constant = 0.3; HFF = 70 Hz.

At the age of 20 this patient received deep brain stimulation (DBS) to the anterior nucleus (AN) of the thalamus (patient AN3 in Andrade et al.).[2] The surgical procedure for the insertion of DBS electrodes and implantable pulse generators has been previously described.[2] Electrode positioning was verified by postoperative MRI. Activation and programming of the stimulators started one month after the electrodes were implanted. The patient was treated with carbamazepine and vigabatrin without dose changes from 3 months prior until 2 years after the surgery.

The frequency of 2ly GTC seizures decreased from 125 per month prior to AN DBS implantation to 60 per month one year after active stimulation. After 4 years of treatment with AN DBS, the frequency decreased further to 45.7 seizures per month. The number of CPS decreased from 4–5 per day to 2–3 per week at 2 years follow up. The patient's diagnosis was unclear until microarray analysis was performed at age 35 and showed a clinically significant 0.641 Mb duplication in chromosome region Xq28 that overlaps with the MECP2 duplication syndrome region.

2. Discussion

Over 90% of patients with MECP2 duplication syndrome who survive into adolescence have epilepsy.[3] The seizure types observed in MECP2 duplication syndrome are variable: GTC, tonic, atonic, atypical absence, focal onset with or without 2ly GTC, reflex, myoclonic and myoclonic-astatic. The EEG pattern can be characterized by slowing or absence of the occipital dominant rhythm as well as paroxysmal rhythmic slow theta activity in the posterior regions. The epileptiform patterns found in these patients are multifocal independent spike discharges and/or generalized spike and slow wave activity.[1,3,4] Seizures resistant to pharmacotherapy or ketogenic diet were reported in approximately 50% of all cases.[1,4]

Our patient is the oldest patient with well-described seizures reported in the literature. His seizure types and interictal EEG are in accordance with those described in the literature. Importantly, this is the first report on the use of DBS for seizure control in MECP2 duplication syndrome. When DBS electrodes were initially implanted in our patient 15 years ago the diagnosis of MECP2 duplication was not known. The reduction in seizure frequency of more than 50% after electrode implantation and stimulation was statistically significant. Importantly, this reduction enabled the patient to have 1 or 2 day long periods of seizure freedom that did not occur before DBS and were considered a significant improvement for him and his caregivers. The reduction in seizure frequency has been maintained over the years (batteries were recently replaced).

The majority of seizure reduction occurred within the first month of implantation before the electrodes were activated. This suggests that the beneficial effect of DBS in this patient may have been related to the microthalamotomy caused by electrode insertion. However, seizure frequency continued to decline over the next years suggesting that the combination of microthalamotomy and chronic stimulation were responsible for the long-term benefits observed following AN DBS. Although the number of antiepileptic drugs was decreased after AN DBS the patient could not be completely weaned and therefore AN DBS was not sufficient on its own in maintaining the improved level of seizure control.

To the best of the authors' knowledge, this is the only MECP2 duplication case to have received DBS. Therefore it is not known

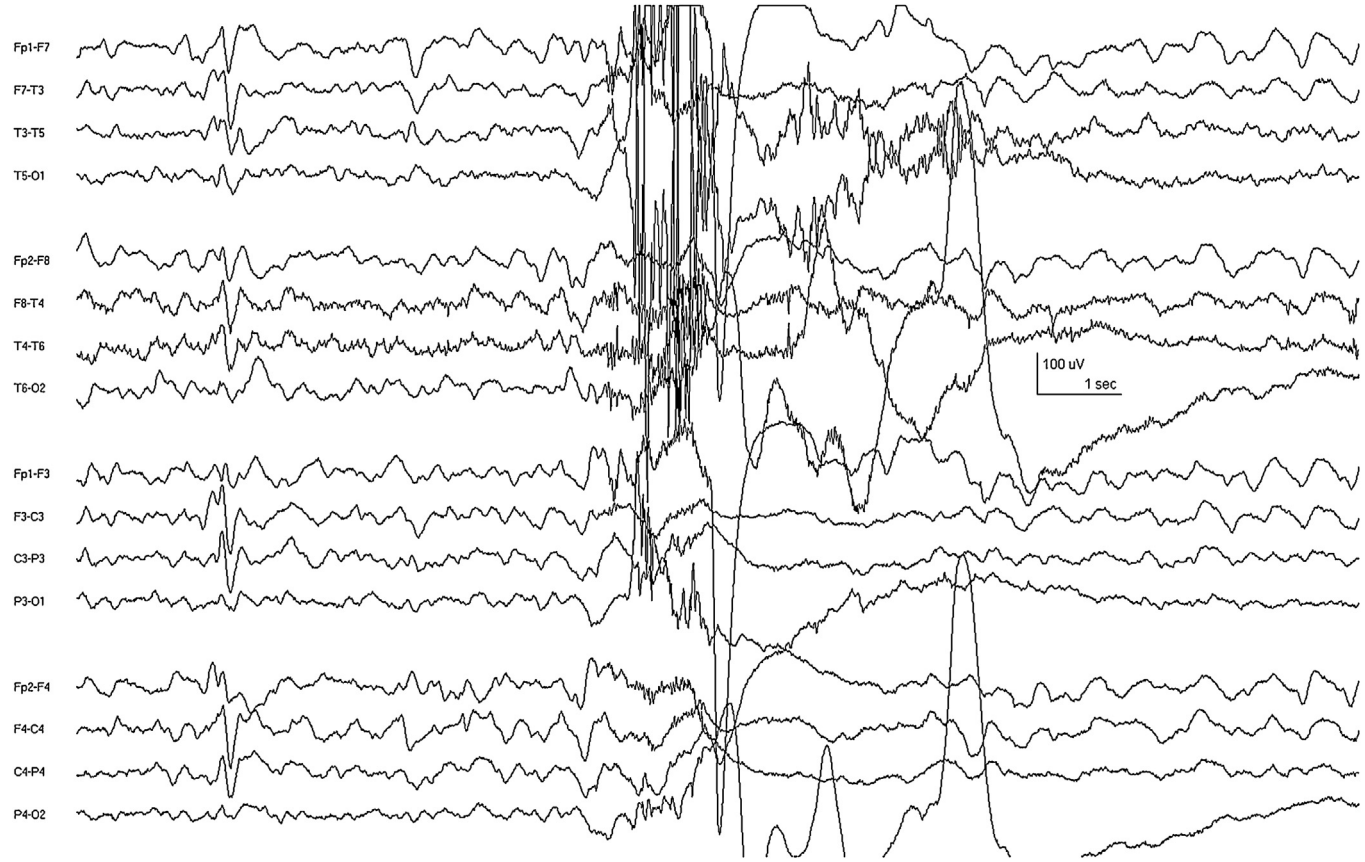

Fig. 2. Atonic seizure; clinical onset in middle of figure marked by muscle and movement artifact, brief EEG attenuation followed by rhythmic frontally predominant delta slow wave activity. Bipolar anterior–posterior longitudinal montage. Time constant = 0.3; HFF = 70 Hz.

whether other patients with MECP2 duplication syndrome will have a significant response to DBS. Our patient experienced improvements in the control of both generalized and partial seizures with and without secondary generalization. However, AN DBS might be preferentially effective for controlling certain types of seizures (for instance, focal onset seizures may respond better to AN DBS, whereas generalized onset seizures may respond better to centro-median thalamic nuclei DBS) and may thus be more effective for specific sub-groups of this patient population. Further studies are needed to confirm our observations.

Conflict of interest statement

Co-author RW has served as a consultant for Medtronic, Inc. The remaining authors have no conflicts of interest.

Acknowledgement

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