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Case Report

Successful corpus callosotomy for post-encephalopathic refractory epilepsy in a patient with *MECP2* duplication syndrome

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Abstract

Background: Patients with *MECP2* duplication syndrome present with distinct facial anomalies and clinical features such as global developmental delay, recurrent respiratory infections, and epileptic seizures. Approximately half of all patients develop epileptic seizures which are refractory in most cases despite active medical management. Furthermore, no previous reports have discussed the efficacy of surgical treatment for seizures in patients with *MECP2* duplication syndrome.

Case report: In the present report, we describe a case of *MECP2* duplication syndrome in a 15-year-old boy who developed epileptic seizures following influenza-associated acute encephalitis. His frequent epileptic spasms, tonic, atonic, and partial seizures were refractory to multiple antiepileptic medications. Electroencephalography revealed continuous diffuse epileptic discharge, resulting in regression. A total corpus callosotomy (CC) was performed at the age of 14 years and 7 months. His seizures markedly decreased following CC, although he continued to experience brief partial seizures approximately once per month. Postoperative examination revealed that his epileptic discharges had disappeared, and that his developmental state had returned to pre-encephalopathy levels.

Conclusion: Our findings indicate that CC may represent a valuable surgical option for children with medically refractory generalized seizures following acute encephalopathy, irrespective of genetic disorders such as *MECP2* duplication syndrome.

Keywords: *MECP2* duplication syndrome; Post-encephalopathic epilepsy; Epilepsy surgery; Corpus callosotomy; Acute encephalopathy

1. Introduction

Mutation of methyl CpG banding protein 2 (MECP2), encoded by the *MECP2* gene on chromosome band Xq28, was identified as the major cause of Rett syndrome in 1999 [1]. Subsequent studies have established that *MECP2* duplication may account for approximately 1% of unexplained X-linked intellectual disability in male patients [2]. Cardinal phenotypes of *MECP2* duplication syndrome include hypotonia, global developmental delay, recurrent respiratory infections, epilepsy, and gastrointestinal symptoms [3]. Nearly 50% of affected individuals develop epilepsy,

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and both generalized and focal seizures are often refractory despite active treatment with multiple antiepileptic medications [3–5]. To our knowledge, no previous reports have discussed the efficacy of surgical treatment for seizures in patients with *MECP2* duplication syndrome.

Corpus callosotomy (CC) is a valuable palliative surgical option for cases of medically refractory epilepsy, especially in cases patients who experience drop attacks [6,7]. CC is typically performed in patients with generalized seizures due to diffuse or multifocal epileptic discharge [7]. However, few reports have documented the efficacy of CC for post-encephalopathic epilepsy [8,9].

In the present report, we discuss the case of a child with *MECP2* duplication syndrome who developed refractory seizures following influenza-associated acute encephalopathy. In this patient, seizure frequency was markedly decreased following CC.

2. Case report

A 15-year-old boy with severe mental retardation and chronic constipation, which he had experienced since infancy, was referred to our hospital for epilepsy evaluation. He was born at full-term via spontaneous vaginal delivery to unrelated healthy parents. At the age of 5 years and 9 months, array comparative genomic hybridization (CGH) analysis and consecutive fluorescent *in situ* hybridization analyses revealed duplication of the *MECP2* gene region on chromosome band Xq28.

At the age of 12 years, he began to experience partial seizures once every few months. We observed him without any antiepileptic medications due to low frequency and short duration of his seizures. He contracted influenza A at the age of 13 years and 10 months. For two days, he exhibited very little response to environmental stimuli and was thus hospitalized. His electroencephalogram (EEG) demonstrated generalized high-amplitude slow wave bursts, while brain MRI revealed abnormal hyperintensities in the left insular cortex and surrounding white matter (Fig. 1). Moreover, T2-weighted images revealed abnormal cystic hyperintensities in the periventricular white matter, which were not prominent at the age of 1 year. He was diagnosed with acute encephalopathy and underwent methylprednisolone pulse therapy (1 g/day for 3 days), following which his consciousness improved. Brief tonic seizures (TSs) and facial clonic seizures appeared soon after discharge. He developed complex partial seizures (CPSs) and epileptic spasms (ESs) in turn, and the seizures were extremely refractory to multiple antiepileptic medications, including zonisamide, levetiracetam, valproate, clobazam, phenytoin, and rufinamide. He eventually experienced regression, loss of walking and vocalization abilities, and drop attacks, which resulted in facial injury.

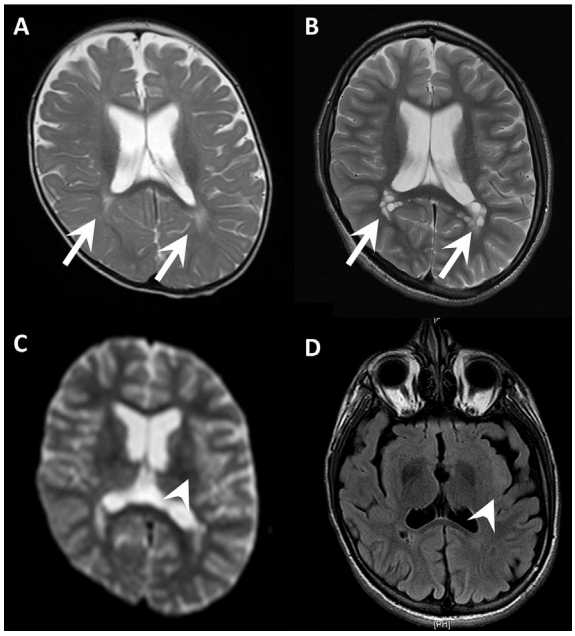

Fig. 1. MRI findings at the age of 1 year (A), 13 years and 10 months (B, C), and 14 years and 5 months (D). (A) T2-weighted imaging revealed mild hyperintensities involving the posterior periventricular white matter (arrow). (B) T2-weighted imaging on day 4 after the onset of acute encephalopathy revealed cystic hyperintensities involving posterior periventricular white matter (arrow). (C) An apparent diffusion coefficient map showing abnormal hyperintensity involving the left insular cortex (arrowhead): this abnormal hyperintensity was observed even 7 months later on fluid-attenuated inversion recovery imaging (D).

He underwent scalp video EEG monitoring for 40 h at our institution, which revealed persistent, diffuse, and anterior dominant 1.5 to 2 Hz high-amplitude spike and wave complex and frequent seizures. During the examination period, he experienced up to 60 total seizures, including TSs, ESs, and atonic seizures (Fig. 2). His parents declined diet therapy. The patient subsequently underwent a complete CC at the age of 14 years and 10 months. He did not exhibit any dysfunctions due to the callosal disconnection syndrome. His seizures markedly decreased following CC. Two months after CC, he underwent scalp video EEG monitoring for 36 h, during which no seizures or persistent epileptiform discharges were observed. However, scarce discharge remained during sleep (Fig. 3). Consequently, he gradually regained walking and vocalization abilities, and antiepileptic medications were successfully reduced. For eight months following CC, his seizures had not been worsened, although he continued to experience brief partial seizures approximately twice per month.

3. Discussion

Our patient with *MECP2* duplication syndrome developed frequent epileptic seizures (including TSs,

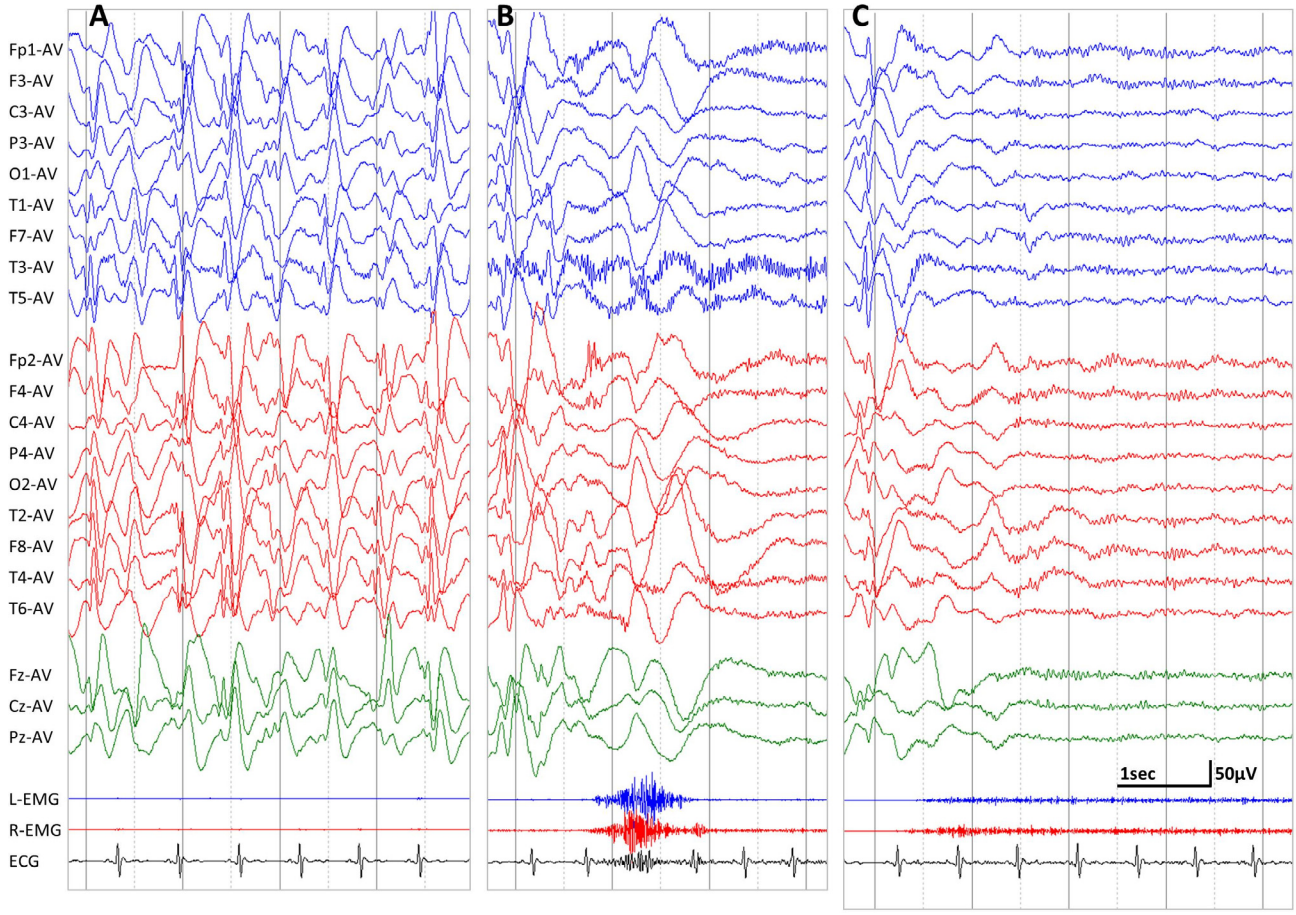

Fig. 2. Scalp EEGs at the age of 14 years and 5 months, prior to corpus callosotomy. (A) Interictal EEG showing persistent, diffuse, anterior-dominant, high-amplitude spike and wave complexes of 1.5 to 2 Hz. (B) Ictal EEG recorded during an epileptic spasm revealed anterior-dominant triphasic slow waves, which were associated with crescendo-decrescendo patterns in electromyography (EMG). (C) Ictal EEG recorded during a tonic seizure revealed prolonged bilateral EMG activity accompanyied by anterior-dominant fast wave activity.

ESs, atonic seizures, and CPSs) following influenza-associated acute encephalopathy. Although his seizures were extremely refractory to multiple antiepileptic medications, they mostly resolved after total CC, and his developmental status recovered as well.

Approximately half of all patients with *MECP2* duplication syndrome develop epileptic seizures by the age of 9 years, including ESs, TSs, absences, myoclonic seizures, and partial seizures. Such seizures are often refractory despite active medical management [3–5], and the efficacy of surgical treatment in patients with *MECP2* duplication syndrome has yet to be reported. *MECP2* duplication syndrome is associated with an increased risk of recurrent respiratory infections, although no reports have discussed the risk of encephalopathy. Post-encephalopathic epilepsy is a well-recognized complication of acute encephalopathy and is refractory in the majority of cases [8–10].

CC is a palliative surgical option for cases of medically refractory epilepsy in patients without resectable epileptic foci [6]. While CC is known to alleviate various types of seizures, particularly drop attacks and generalized seizures, few reports have discussed the efficacy of CC for post-encephalopathic epileptic seizures [8,9].

While periventricular abnormalities may have been associated with *MECP2* duplication syndrome in the present case [11], the left insular lesion may have been associated with acute encephalopathy. Post-encephalopathic "symptomatic" epilepsy typically occurs in patients with brain MRI insults [8–10], and the specific seizure types may result from the pattern of brain injury. Our patient first presented with partial seizures, following which he developed post-encephalopathic ESs, TSs and atonic seizures, suggestive of cortical-subcortical interaction [12]. In addition, whereas ESs, TSs and atonic seizures were eliminated after total CC, partial seizures which were present prior to the encephalopathy were remained. We hypothesize that acute encephalopathy elicited the involvement of the insular cortex and surrounding white matter. Abnormal neuronal networks involving the cortical and subcortical structures constructed during the recovery period may have resulted in ESs and TSs. CC may have eliminated these seizures by dismantling the abnormal

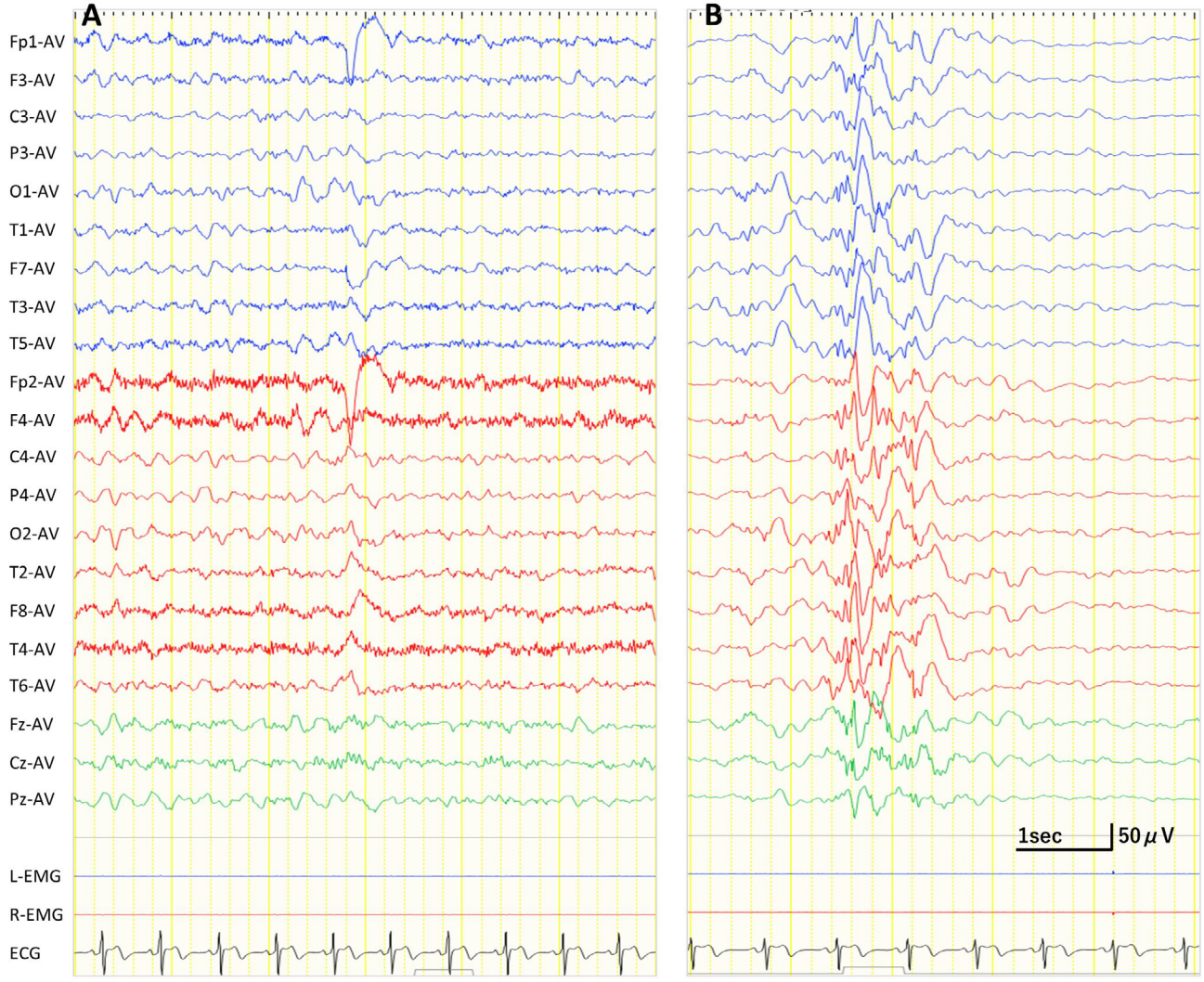

Fig. 3. Scalp EEGs 2 months after corpus callosotomy. (A) EEG showing no epileptiform discharges during the waking state. (B) Diffuse polyspikes and wave bursts were scarcely observed during sleep.

networks. Nonetheless, the efficacy of CC for drug-resistant epilepsy in patients with *MECP2* duplication syndrome remains unclear.

In conclusion, our findings indicate that CC may represent a valuable surgical option for children with medically refractory generalized seizures following acute encephalopathy, irrespective of genetic disorders such as *MECP2* duplication syndrome.

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