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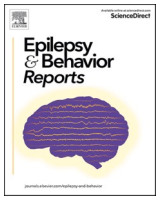

Total callosotomy ameliorates epileptic activity and improves cognitive function in a patient with Miller-Dieker syndrome

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ABSTRACT

Miller-Dieker syndrome (MDS) is characterized by facial abnormalities and lissencephaly and is caused by a microdeletion in the region containing the *LIS1* gene at chromosome 17p13.3. We report a case in which postnatal neuroimaging revealed severe lissencephaly. A 9-month-old boy presented with infantile spasms syndrome. Because of the refractory course of seizures and continued poor vitality, total corpus callosotomy was performed at 28 months of age. Intraoperative electroencephalogram (EEG) showed that the bilateral synchronous epileptiform discharges disappeared immediately after the disconnection. Postoperatively, the epileptic spasms (ES) in clusters disappeared, and single ES followed by focal seizures became the main symptom. The patient smiled more and became more responsive to stimuli. Postoperative scalp interictal EEG showed desynchronized multifocal spike and wave discharges with a marked decrease in the bilateral synchronous spike and wave discharges. Our findings suggest that the corpus callosum is involved in the mechanism ES in clusters in MDS-associated lissencephaly, and total callosotomy could be a therapeutic option.

1. Introduction

Miller-Dieker syndrome (MDS) is characterized by lissencephaly and facial abnormalities, including a small broad forehead, temporal depression, square face, short and small nose, upturned nostrils, thin upper lip, small jaw, and low auricles [1]. MDS is caused by a microdeletion in the region containing the *YWHAE* and *LIS1* genes at chromosome 17p13.3. Abnormalities in the layered structure of the cerebral cortex occur due to haploinsufficiency of *LIS1* [2,3]. MDS has a high incidence of epilepsy associated with underlying lissencephaly, and many patients present with infantile spasms syndrome [4], the main treatment for which is medication, and surgical treatment is considered in cases with a drug-resistant course. Corpus callosotomy (CC), a type of surgical treatment for epilepsy, is effective in treating infantile spasms syndrome, especially in cases without lesions on magnetic resonance imaging (MRI), but reports on cases with extensive cortical dysplasia, such as lissencephaly, are rare [5,6]. This study aimed to evaluate the efficacy of CC for MDS-associated infantile spasms syndrome by assessing in the pre-, intra-, and postoperative EEG.

2. Case presentation

The patient was born weighing 975 g, at 30 weeks of gestation via emergency cesarean section owing to non-reassuring fetal status. Family history was unremarkable. The patient had a peculiar facial appearance with a small head, jaw, and nose and low auricular position. MRI, taken at 76 days of age, showed severe lissencephaly. Comparative genomic hybridization showed deletion in the 17p13.3-p13.2 region that contains the *LIS1* and *YWHAE* genes, and Miller-Dieker syndrome was diagnosed. Focal impaired awareness seizures with apnea and behavioral arrest, were observed at the age of 6 months. These were resolved after phenobarbital administration. Spasm-like movements appeared in clusters at the age of 9 months. Interictal EEG indicated hypsarrhythmia, and ictal EEG showed generalized irregular high-amplitude slow waves accompanied by limb elevation, indicating epileptic spasms (ES). Based on these findings, the patient was diagnosed with infantile spasms syndrome. Various antiepileptic drugs, such as valproate, topiramate and levetiracetam, were ineffective, and adrenocorticotropic hormone (ACTH) and ketogenic diet therapies were initiated, but spasms

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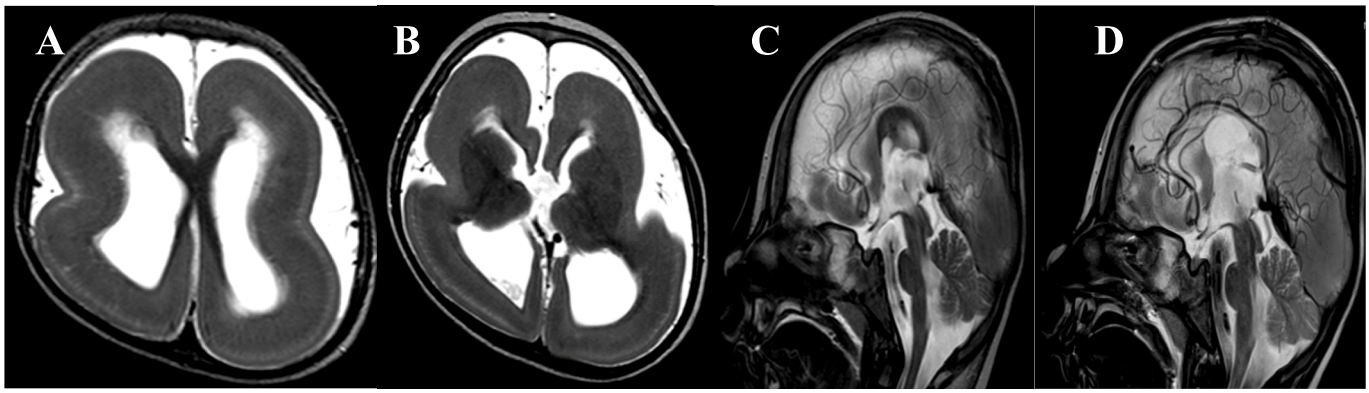

Fig. 1. Head T2-weighted magnetic resonance imaging (T2WI MRI). Preoperative axial MRI, showing a four-layered cortex with a cell-sparse layer and no brain gyri (A and B). Preoperative sagittal MRI showing a short and thick corpus callosum (C). Postoperative MRI showing a completely dissected corpus callosum (D).

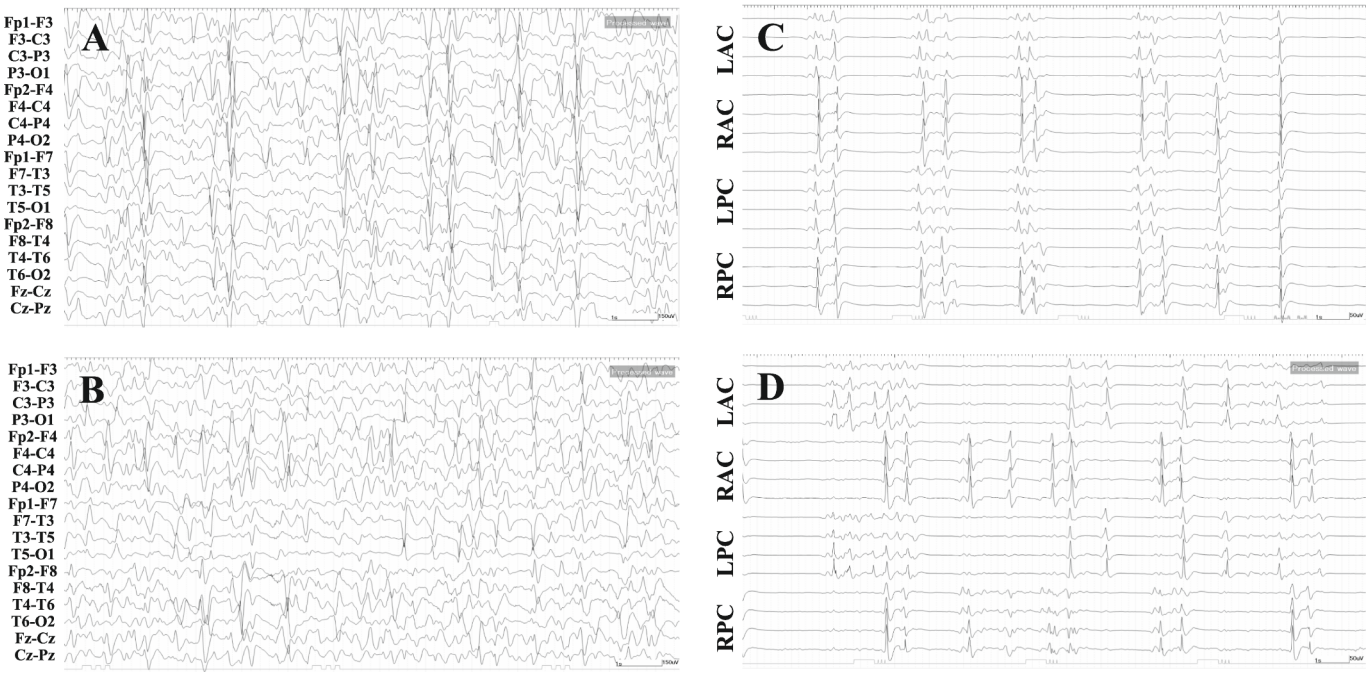

Fig. 2. Scalp electroencephalogram (EEG) and intraoperative EEG findings. Scalp EEG during sleep (A and B): preoperative, high-amplitude, bilateral synchronous spike-and-wave (A); desynchronized multifocal spike-and-wave with a marked decrease in the bilateral synchronous spike-and-wave after surgery. (B). Intraoperative EEG findings are shown in C and D. Bilaterally synchronous epileptiform discharges were seen almost continuously before disconnection (C). In contrast, the bilaterally synchronized epileptiform discharges largely disappeared, but the asynchronous multifocal spikes remained after disconnection (D). LAC: left anterior cortexes, RAC: right anterior cortexes, LPC: left posterior cortexes, RPC: right posterior cortexes.

continued and hypsarrhythmia did not resolve. Tube feeding became necessary at the age of ten months, and a tracheostomy was performed due to repeated aspiration pneumonia. At 1 year, the patient had no neck control, no verbal comprehension, and severe intellectual disability.

At 2 years of age, he had 4–5 clusters of ES per day despite increased use of antiepileptic drugs such as clobazam, zonisamide, and rufinamide. Vigabatrin was not approved for use in Japan at that time and hence, was not administered. We considered surgical treatment because he had a refractory course. MRI at 2 years of age showed a short and thick corpus callosum (Fig. 1), and ^{123}I-iomazenil single-photon emission computed tomography showed no focal decrease in isotope accumulation. Scalp EEG showed frequent, high voltage, bilateral diffuse spike and wave discharges (Fig. 2A). It was judged that a radical resection was unlikely to result in seizure improvement without significant morbidity. The patient was considered for a palliative surgical therapy to alleviate the seizures. The seizure improvement rate was considered to be higher with total CC than with anterior CC, and the risk of permanent disability was low for CC; hence, total CC was performed at the age of two years and four months. Intraoperative EEG was planned under general anesthesia with 2.5 % sevoflurane to evaluate the cortical EEG activity before and after the corpus callosum dissection. Sixteen electrodes were placed over the left, right, anterior, and posterior cortexes, and recordings were made when no surgical activities were being performed. Bilaterally synchronous epileptiform discharges, which were observed almost continuously before the disconnection (Fig. 2C), almost disappeared after total disconnection; asynchronous multifocal spikes remained (Fig. 2D).

The ES clusters disappeared postoperatively. A combined seizure with ES followed by a focal onset tonic seizure became the main symptom. No functional impairment was observed postoperatively. In terms of cognition, the patient smiled more often and was more responsive to stimuli. The bilateral synchronous spike-and-wave was markedly reduced, and desynchronized multifocal spike-and-wave was

observed (Fig. 2B).

Three years after the surgery, seizures occurred only a few times per day, with ES followed by focal tonic seizures with extremities. ES rarely appeared in clusters. He has not achieved any noticeable gains in developmental indicators, but he has maintained positive cognitive and emotional influences, such as smiling and improved responsiveness to stimuli. Parental satisfaction with the total CC was good. We provided informed consent to the parents of the patient for publication of this report.

3. Discussion

To the best of our knowledge, this is the first report of a patient undergoing total CC for infantile spasms syndrome caused by MDS-associated lissencephaly. The patient underwent total CC, with recorded pre-, intra-, and post-operative EEG. Postoperatively, seizures decreased, vitality improved, and EEG was desynchronized and with decreased epileptiform activity.

The therapeutic outcome of CC in infantile spasms syndrome has been reported in several studies [5,6]. Pinard JM et al. reported better postoperative results with total CC than with anterior or posterior callosotomy, with ES resolved in 80 % of cases. [5] Baba et al. also reported resolution of ES in 42.9 % of patients. [6] In general, CC has been shown to have therapeutic effects on ES.

Epilepsy caused by lissencephaly is likely to have an intractable course [7,8]. However, such patients are not good candidates for surgical treatment because of their poor seizure prognosis due to the strong structural, pathological, and molecular epileptogenicity throughout the brain. This case corresponded to the most severe imaging classification Type 1 reported by Dobyns et al. [9] Kawai et al. reported the usefulness of callosotomy, mainly for reducing the seizures in patients with widespread bilateral dysplasia. [10] They described one case as a Type 1 lissencephaly, but ES was not mentioned as a seizure type, and the patient did not present agyria. They reported that the seizure reduction was maintained for about two years after surgery. [10] However, no genetic assessment was described in these studies, and MDS was not diagnosed.

The epileptic EEG activity was reduced in our patient, and even became left–right asynchronous after total CC. In the case reported by Kamida et al. the two-week postoperative evaluation showed marked improvement in epileptic EEG activity, with only unilateral focal EEG abnormalities remaining. [11] Intraoperative EEG findings showed left–right desynchronization immediately after dissection, suggesting that the corpus callosum is involved in the lissencephaly epileptic EEG activity formation in MDS. Additionally, total CC markedly reduced the number of ES in clusters, suggesting that the corpus callosum is involved in the mechanism of ES in clusters in MDS. However, since single ES followed by focal seizures persisted, pathways involving the left or right hemisphere, subcortical structures, and the brainstem might still be present.

The limitation of this study is that only one case was reported. Further accumulation of cases is required to confirm whether total CC could be a therapeutic option for West syndrome associated with MDS.

Ethical Statement

This work was supported by MHLW Research program on rare and intractable diseases, Grant number JPMH23FC1013.We obtain informed consent from the parents of a patient.

CRediT authorship contribution statement

Masataka Fukuoka: Writing – original draft, Conceptualization. **Ichiro Kuki:** Writing – review & editing, Conceptualization. **Yuka Hattori:** Data curation. **Hitomi Tsuji:** Data curation. **Asako Horino:** Data curation. **Megumi Nukui:** Data curation. **Takeshi Inoue:** Data curation. **Shin Okazaki:** Data curation. **Noritsugu Kunihiro:** Data curation. **Takehiro Uda:** Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contributors' Statement

Masataka Fukuoka and Ichiro Kuki conceptualized and designed the report, wrote the manuscript, and were responsible for all stages of the report. Yuka Hattori, Hitomi Tsuji, Asako Horino, Megumi Nukui, and Takeshi Inoue were the attending doctors for the patient and were responsible for collection of the data. Shin Okazaki critically revised the manuscript for important intellectual content and helped to draft the manuscript. Noritsugu Kunihiro and Takehiro Uda performed surgical treatment. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2024.100670.

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