



Case Report

Periodic discharges with high frequency oscillations recorded from a cerebellar gangliocytoma in an epileptic infant

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ABSTRACT

Background: Subcortical epilepsies associated with developmental tumors in the cerebellum are rarely experienced. As supportive evidence of the intrinsic epileptogenicity of cerebellar tumors, previous electroencephalogram (EEG) studies with intratumoral depth electrodes demonstrated epileptiform or ictal discharges. Recent studies have demonstrated that high frequency oscillations (HFOs) can be regarded as a new biomarker of epileptogenesis and ictogenesis; however, there are few evidence about HFOs in cases of epilepsy associated with cerebellar tumors.

Case Description: A 6-month-old Japanese male infant presented to our hospital with drug resistant epilepsy. We underwent subtotal resection of a cerebellar gangliocytoma and obtained good seizure outcomes. Intraoperative EEG in the tumor depicted HFOs in the form of ripples, riding on periodic discharges.

Conclusion: Our findings provide further supportive evidence for the intrinsic epileptogenicity of cerebellar tumors.

Keywords: Cerebellar epilepsy, Depth electrode, High frequency oscillations, Intrinsic epileptogenicity, Subcortical epilepsy

INTRODUCTION

Classical teaching in epileptology localizes the origin of focal seizures solely in the cerebral cortex; however, recent electrophysiological and neuroimaging studies have provided evidence for the initiation of epileptic seizures within subcortical structures.^[6,13] The intrinsic epileptogenicity of hypothalamic hamartomas, for instance, has supported the presence of subcortical epilepsies.^[11,15] Subcortical structures make widespread connections with the cerebral cortex and harbor the potential to synchronize, modulate, or disrupt normal cortical activity, suggesting that they are not mere bystanders of epileptic networks and, in fact, may cause epilepsy.^[6,13] An important step toward uncovering the existence of subcortical epilepsies was the identification of distinct

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epileptic syndromes associated with a developmental tumor, including ganglioglioma/gangliocytoma or hamartoma, in the cerebellum.^[6,13] As of 2017, 31 cases of epileptic patients with cerebellar tumors have been reported.^[6] As supportive evidence of intrinsic epileptogenicity of these cerebellar tumors, previous electroencephalogram (EEG) studies demonstrated epileptiform or ictal discharges in the lesion, which were recorded with depth electrodes.^[1,2,5,6,8,9,12,14,17,19]

High frequency oscillations (HFOs) are a form of brain activity observed in EEG in the frequency range of 80–500 Hz. HFOs can be classified into ripples (80–200 Hz) and fast ripples (200–500 Hz) on the basis of their distinctive characteristics. Recent studies have reported that both ripples and fast ripples can be regarded as new biomarkers of epileptogenesis and ictogenesis.^[14,15] We surgically treated a 6-month-old epileptic infant with cerebellar gangliocytoma, and intraoperative EEG with intratumoral depth electrode showed periodic discharges with HFOs. We describe the detailed EEG findings of this case and demonstrate further supportive evidence for the intrinsic epileptogenicity of cerebellar tumors.

CASE REPORT

This male infant was diagnosed with mild ventriculomegaly on prenatal ultrasound examination. He was born at 39 weeks and 1 day of gestation with an uneventful delivery. Magnetic resonance (MR) images at the age of 3 days revealed a tumor in the right cerebellum protruding into the 4th ventricle. Conservative follow-up was selected because he was asymptomatic. However, 2 weeks after birth, he developed epileptic seizures starting with horizontal nystagmus and conjugate deviation to the right side, followed by tonic-clonic seizures of his left upper limb. His seizure frequency was 4–5 times/h. Optimal doses of antiepileptic drugs including phenobarbital, levetiracetam, perampanel, and topiramate were administered. His seizure frequency was reduced to 1–2 times/h; however, complete control could not be obtained.

The patient was referred to us at the age of 3 months. His height and body weight were 65.4 cm and 7.1 kg, respectively, which were age-appropriate. During the interictal state, his neurological findings were normal. His seizure began with the twitching of the bilateral eyelid, horizontal nystagmus, and ocular displacement lasting 10 s to 1 min and was sometimes followed by tonic seizures in his right upper and lower limbs. Interictal EEG revealed periodic discharges with a predominant negative component occurring once every 1–4 s in the left and mid-occipital regions (O1 and Oz of the International EEG 10–20 system, respectively) [Figure 1a]. Ictal EEG demonstrated rhythmic slow waves originating from the occipital region (O1, O2, and Oz) [Figure 1b]. MR images demonstrated an isointense tumor, with a size of 15 × 16 × 23 mm (same size as MR images at

the age of 3 days) in the right cerebellum protruding into the 4th ventricle [Figure 1c and d]. No gadolinium enhancement was noted. ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed hypermetabolism of the tumor [Figure 1e].

At 6 months of age, surgery was performed under general propofol anesthesia. Through the trans-cerebellomedullary fissure approach, a slightly whitish tumor protruding into the 4th ventricle was exposed [Figure 2a]. A depth electrode with 3 contacts (0.5 cm distance between each contact) was inserted into the tumor, and a strip electrode was placed on the cerebellar surface [Figure 2b]. EEG recorded in the tumor depicted periodic discharges with a positive-negative configuration occurring once every 1–4 s [Figure 2c]. The periodic discharges showed maximum amplitude at a depth of 10 mm from the tumor surface, with a slight decrease in amplitude at 5 and 15 mm depths. HFO analysis was performed using a time-frequency analysis (short-term fast Fourier transformation) using an EEG system manufactured by Nihon Kohden (Tokyo, Japan). The spectral power was calculated for the frequency range of 0–200 Hz in 2 Hz steps. Activity at around 80–100 Hz (ripple range), riding on the periodic discharges, was detected [Figure 2d]. No paroxysmal discharge was recorded from the cerebellar surface [Figure 2e]. The tumor was carefully excised to avoid damage to the 4th ventricular floor. When three-quarters of the tumor was resected, the tip of the depth electrode was inserted again into the remnant tumor, and disappearance of the paroxysmal activity was observed [Figure 2f]. We repeatedly confirmed that no paroxysmal discharge was recorded from the cerebellar surface [Figure 2g]. Subtotal resection of the tumor, leaving the tumor around the right facial colliculus, was performed, which was confirmed with postoperative MR images [Figure 2h].

The postoperative course was uneventful. The patient was seizure-free within 2 years following the operation, even after reduced dosages of antiepileptic drugs. Postoperative EEG demonstrated the disappearance of paroxysmal activity. Histopathologically, the tumor consisted of irregularly clustered neuronal nuclei (NeuN) immunopositive ganglion cells without a glioma component, indicating gangliocytoma [Figures 2 i and j].

DISCUSSION

Previous authors have demonstrated, with the use of perioperative depth recording, the existence of ictal discharges originating from a tumor^[2,5,6,8,14,17] or direct electrophysiological correlation between intratumoral paroxysmal discharges and electromyographic discharges in myoclonic seizures^[1,9] or hemifacial seizures.^[10,19] Since chronic implantation of an intratumoral depth electrode was thought to be too invasive for a 6-month-old infant, we

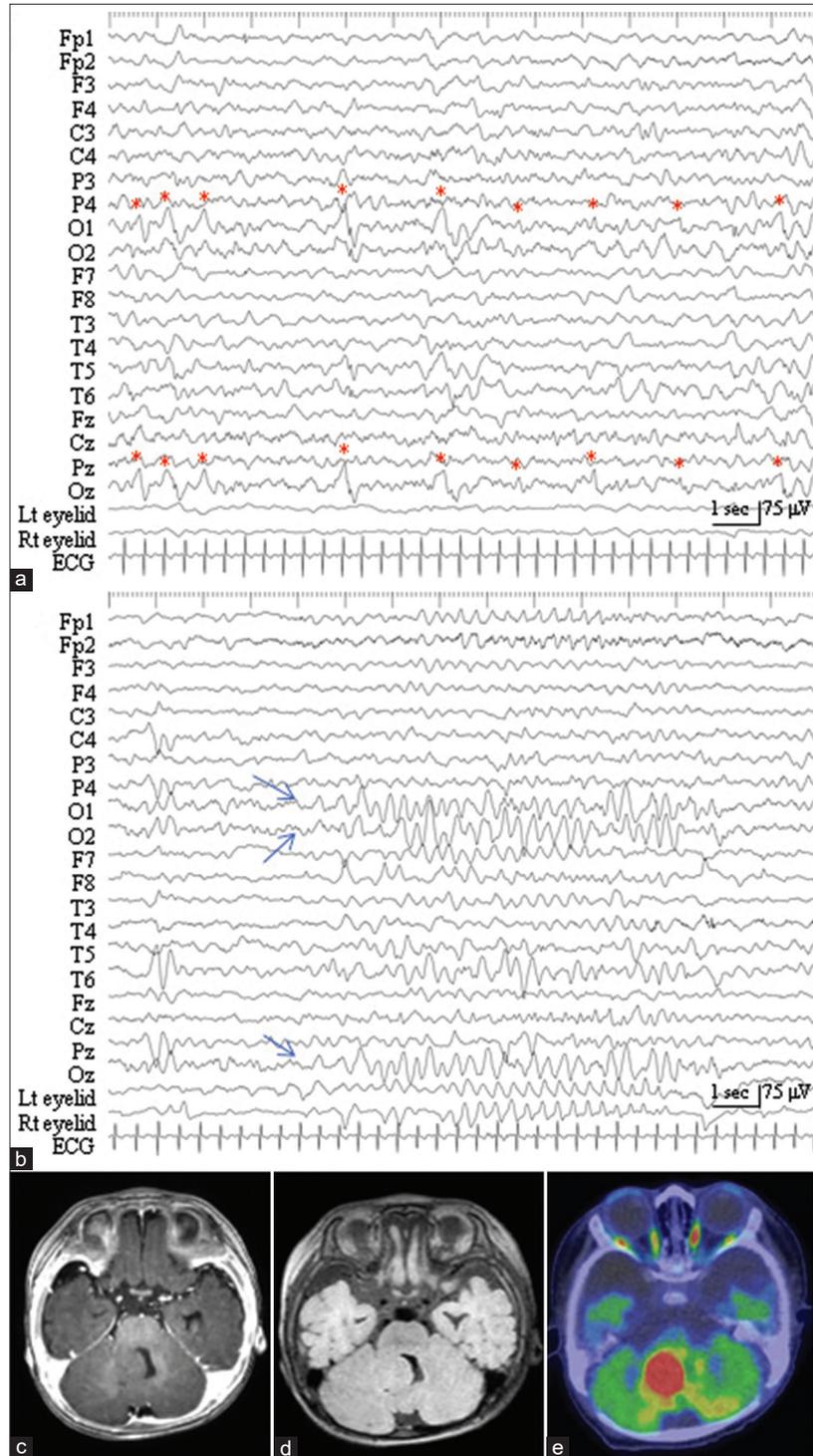


Figure 1: (a) Interictal electroencephalogram (EEG), with an averaged reference, reveals periodic discharges with a predominant negative component occurring once every 1–4 s in the left and mid-occipital region (O1 and Oz of the International EEG 10–20 system, respectively, red asterisks). (b) Ictal EEG, with the twitching of bilateral eyelids, demonstrates rhythmic slow waves originating from the occipital region (O1, O2, and Oz, blue arrows). (c) Preoperative axial-view of T1-weighted (Gd) administration shows an isointensity tumor in the right cerebellum protruding into the 4th ventricle. No Gd enhancement was noted. (d) The tumor is presented in an isointense on preoperative axial view of image with fluid level attenuated inversion recovery sequences. (e) Fusion image of ¹⁸F-fluorodeoxyglucose positron emission tomography and computed tomographic scan, at the level comparable to the panel (c), depicts hypermetabolism of the tumor.

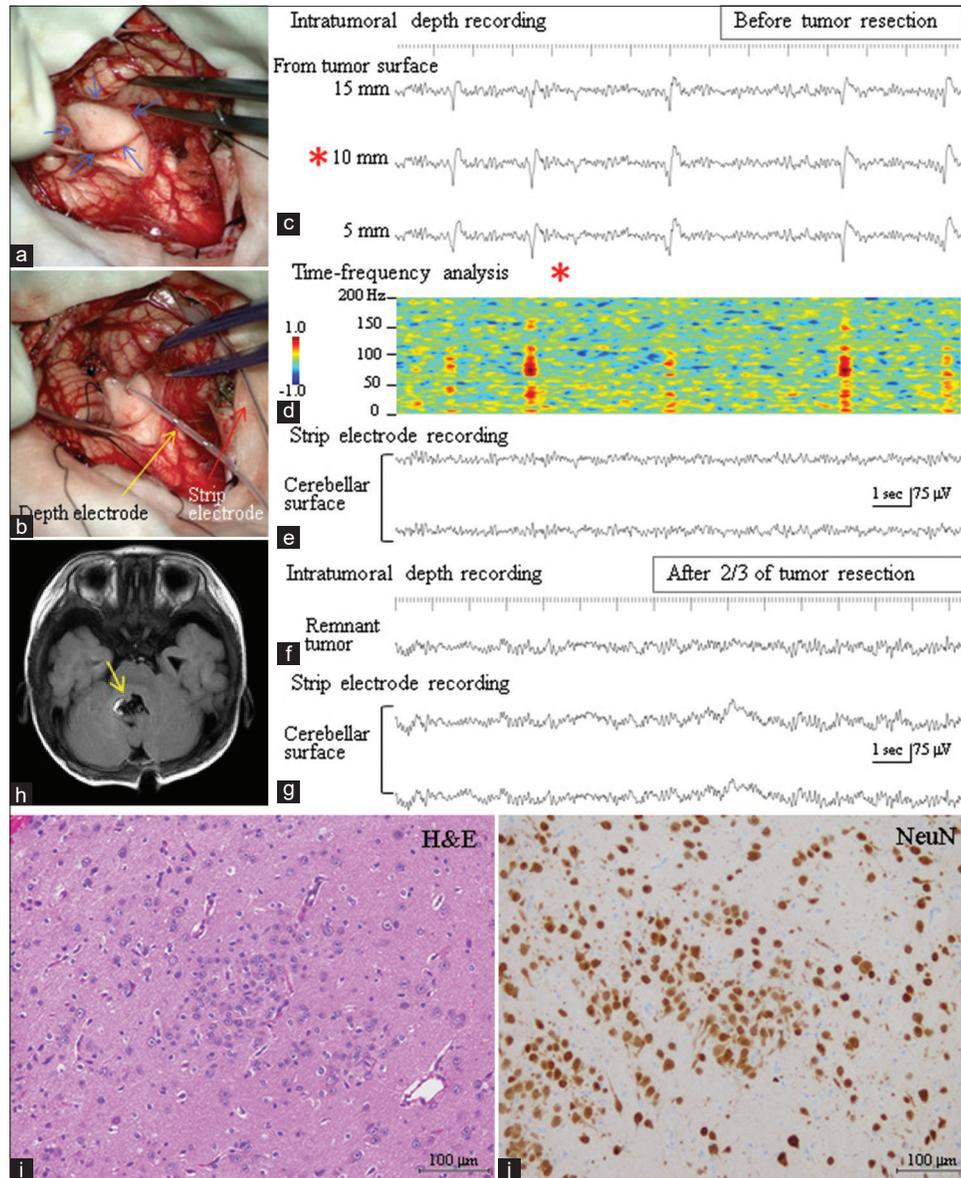


Figure 2: (a) Intraoperative photograph shows that a tumor (blue arrows) protruding into the 4th ventricle is exposed through the transcerebellomedullary fissure approach. (b) A depth electrode with 3 contacts (yellow arrow) is inserted into the tumor, and a strip electrode (red arrow) is placed on the cerebellar surface. (c) Intraoperative depth electroencephalogram (EEG) recording from the tumor, with A1 reference, depicts periodic discharges with a positive-negative configuration occurring once every 1–4 s. The periodic discharges show maximum amplitude at a depth of 10 mm from the tumor surface (red asterisk), with a slight decrease in amplitude at 5 and 15 mm depths. (d) Time-frequency analysis (short-term fast Fourier transformation) for the EEG at a depth of 10 mm from the tumor surface (red asterisk) demonstrates high frequency oscillatory activity around 80–100 Hz (ripple range), riding on the periodic discharges. Color coordinates were constructed on a logarithmic scale (–1.0 to 1.0). (e) No paroxysmal discharge was recorded from the cerebellar surface. (f) Following the resection of three-quarters of the tumor, the tip of the depth electrode was inserted again into the remnant tumor. EEG demonstrates the disappearance of paroxysmal activity from the remnant tumor. (g) No paroxysmal discharge was noted on the cerebellar surface as was observed before resection of the tumor. (h) Postoperative T1-weighted magnetic resonance image demonstrates that the tumor was subtotaly resected except for the tumor around the right facial colliculus (yellow arrow). (i and j) Histopathological findings of the tumor with hematoxylin and eosin staining (i) and immunostaining for neuronal nuclei (NeuN) (j). The tumor consists of irregular clustering of NeuN-immunopositive ganglion cells without a glioma component.

intraoperatively recorded the depth EEG, as was performed by Lascano *et al.*^[12] The recorded periodic discharges were

determined to be interictal EEG findings. Interestingly, the frequency of occurrence of intratumoral periodic discharges

was almost the same as that of preoperative interictal periodic discharges recorded on the scalp-recorded EEG. Although interictal paroxysms are well-characterized electrophysiological signals in the epileptic brain, their sensitivity and specificity in detecting the seizure onset zone remain elusive.^[3,16]

Recent studies reported that interictal HFOs can be regarded as a new biomarker of epileptogenesis and ictogenesis.^[4,7] The relationship between ripple events and epileptogenicity is less clear than that for fast ripple events and epileptogenicity since they can represent both normal physiological activities associated with higher brain function as well as epileptic activity.^[7] However, increased rates of ripple activity have also been described in human epileptogenic tissue.^[3,18] Since the ripple activity was recorded exclusively within the tumor, our findings indicate high epileptogenicity of the tumor rather than normal physiological activity. Related to this finding, in the present case, hypermetabolism of a histologically benign tumor was noted on FDG-PET, which may reflect increased neuronal activity associated with frequent epilepsies, as is previously demonstrated.^[2,9]

Another notable finding was that the periodic discharges with HFOs showed maximum amplitude in the center of the tumor, with a slight decrease in amplitude at the periphery, and were not recorded in the remnant tumor after three-quarters of the tumor was resected. These findings indicate that a tumor of a certain size is needed to cause epileptic activity and support the findings that the subtotal or partial removal of the tumor can cease epileptic seizures.^[6,9,12,17,19] In the present study, a good postoperative seizure outcome was obtained for 2 years, while the tumor around the right facial colliculus was left behind. However, there are also reports of cases requiring additional resection of the residual tumor to obtain complete seizure elimination;^[2,14] therefore, the confirmation of the disappearance of paroxysmal activity with intraoperative depth EEG recordings from the remnant tumor, as was performed in the present case, might be imperative.

Although our experience is limited to a single case, the finding adds further supportive evidence of intrinsic epileptogenicity of the cerebellar tumor.

Statement of ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient's parents for publication of this case report and any accompanying images.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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