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Abstract

The correlation between scalp EEG, intraoperative electrocorticogram, neuroimaging and histopathology was examined in a epilepsy child with diffuse cortical dysplasia. A 6-year-old girl with moderate mental retardation had suffered from intractable complex partial and generalized epilepsy since 2-year-old. MR images demonstrated unilateral large macrogyria/polymicrogyria and schizencephaly in the right occipital lobe. The epileptic focus was detected on the macrogyria by EEG and single-photon emission tomography. However, intraoperative electrocorticogram showed frequent spikes from the polymicrogyria and no paroxysmal activity in the macrogyria. The polymicrogyria was resected including the macrogyria using an image-guided system. The histological findings revealed that the macrogyria was covered and separated with glial bundles. It has been reported that epileptogenisity was produced from abnormal neurons and their arrangement in cortical dysplasia, however in this case, the major dysplastic lesion had no epileptogenisity, rather the focus might be in polymicrogyria around the lesion.

(144 words)

Introduction

Cortical dysplasia is a disorder of cerebral development and organization, frequently associated with epilepsy. As high-resolution magnetic resonance imaging could visualize small cortical lesions, cortical dysplasia attracted neurosurgeon's attention as a surgical curable epileptic disease. However, surgery for epilepsy associated with widespread or large cortical dysplasia remained difficult. We present successful results in a epilepsy child with widespread cortical dysplasia using combination of intraoperative electrocorticogram (ECoG) and image guided system, and examined the correlation of electroencephalogram (EEG), ECoG, neuroimaging and histopathology.

Case report

A 6-year-old girl with moderate mental retardation was admitted to our hospital to treat intractable epilepsy. She was born by cesarean section at 41 gestational weeks because of cephalopelvic disproportion. She had no abnormal history during fetal period nor neonatal period including febrile convulsion, meningitis and head trauma. There was no family history of epilepsy. At the age of 2 years she experienced the initial seizure, which was upward gazing and hyperventilation with impaired consciousness several seconds in duration. One month later, the frequency of her seizures became seven or eight times everyday. Her mother brought her to a hospital, and a CT scan revealed right occipital schizencephaly. She was diagnosed symptomatic partial epilepsy and medicated with anticonvulsants. However, her seizure could not be suppressed enough, and then she was referred to an epilepsy center at the age of 4 years. Surgical indication to her epilepsy was denied there, and anticonvulsant adjustment temporarily

succeeded to reduce seizures. As the seizure frequency was not improved less than five times a day, she was referred to our hospital to evaluate and control her seizures.

She weighed 20kg and stood 118cm, which appeared normal growth, and had no surface anomalies. Neurological examination revealed no focal deficit except for the left homonymous hemianopsia. Her mental development was retarded, which was corresponded to that of 3 or 4-year-old, and developmental quantity (DQ) was 54 on Tsumori-Isobe's developmental scale. The type of her seizures was complex partial seizures (CPS) and generalized tonic seizure (GTS). She showed sudden hyperventilation with vocalization and following tonic convulsion of limbs, and lasted for a minute or extended to secondary generalization. Another type of CPS was behavioral arrest with left gazing for several ten minutes, and it often developed into status epileptics. GTS was observed most frequently, it showed sudden tonic posture of four limbs with falling and lasted for a few minutes. She has received 175mg of zonisamide and 500mg of valproate per day, and plasma concentrations of them were 27.1mg/dl and 67.7 mg/dl on admission, respectively.

Ictal and interictal EEG

Interictal spikes were recorded diffusely, but dominantly in the right central and parietal regions on a scalp EEG. The epileptic focus was suspected there due to appearance of phase reversal. Ictal EEG was successfully recorded on four times by long-term video/EEG monitoring, however, lateralization and localization of the seizure onset could not be detected. No invasive EEG recording was performed.

Neuroimagings

MR images demonstrated the findings of schizencephaly in the right occipital lobe (Fig. 1). The cleft communicated to the right posterior horn of the hypoplastic lateral

ventricle. The cortical area adjacent to the cleft was consisted of significantly thickened gray matter intensity, which was covered with a thin layer of white matter intensity, and formed macrogyria. The abnormal thick gray matter continued to the right thalamus and hypothalamus. The right hippocampus could not be identified. Polymicrogyria was shown widely in the right temporal and parietal lobe. The sylvian fissure and central sulcus formed a wide and deep fissure, whose surface showed polymicrogyria with thick gray matter. These structural anomalies could be recognized well on 3D-reconstracted MR image (Fig. 1B). There was no abnormality in the left hemisphere except for a mild ventricular enlargement.

On interictal single-photon emission tomography (SPECT) using ^{99m}Tc-ECD, the right occipital lesion showed normal perfusion of the gray matter, and mild low perfusion area was observed in the right frontal and parietal lobes (Fig. 2a). Ictal SPECT revealed marked high perfusion area in the right occipital lesion and adjacent temporal lobe (Fig. 2b).

Operative findings

A large craniotomy exposed the right occipital, parietal and temporal lobes. The schizencephalic cyst was covered with a thick arachnoid membrane, and the cavity was made with an enlarged subarachnoid space communicating to the lateral ventricle. The temporo-occipital macrogyria showed few gyration and yellowish-white surface. The temporal and parietal lobes around the macrogyria showed diffuse polymicrogyria (Fig. 3). ECoG was recorded from the surface of the polymicrogyria and occipital macrogyria. Interictal spikes elicited frequently from the polymicrogyria, although there were no paroxysmal activity in the macrogyria (Fig. 4). The epileptogenic zone of polymicrogyria was resected including the macrogyric lesion. The medial resectable

margin of the lesion was determined using a image-guided system (Viewing Wand, ISG technologies, Toronto, Canada). Following the en bloc resection, the spikes significantly reduced around the resected cavity, and then the surgery was finished.

Histopathology

The surface of macrogyric lesion was covered with the pia matter and a layer of subpial gliosis. There was a myelinated glial layer under the gliosis, which continued to deeper complicated glial bundles (Fig. 5A). Those showed positive stain for any of luxol fast blue, glial fibrillary acidic protein (Fig. 5C) and phosphotungstic acid hematoxylin. The glial bundle separated the gray matter, which appeared like islands (Fig. 5A, B). Even in the glial bundle some neurons were observed. The gray matter islands had no laminar structure and contained numerous neurons. The neurons showed polymorphism and multipolarity (Fig. 5D). Neighboring cortical areas of the lesion showed widely polymicrogyria. Normal cortical laminar structure was maintained there, but, neuronal density was increased than normal cortex.

Postoperative course

The patient tolerated the surgery well and showed no additional neurological deficits postoperatively. During postoperative two weeks, she still exhibited several seizures everyday. Seizures gradually reduced next four weeks and disappeared from the seventh week. Complete seizure free was obtained for postoperative two years receipting the same anticonvulsants as those prior to the surgery.

Discussions

The term of cortical dysplasia is widely used to mean cerebral malformations. It consists of various structural disorders of the brain, including disorganization of the

white matter. Clinical features of them were also different between the patients. Some classifications of cortical dysplasia were proposed as based on the findings of neuroimaging and/or histological characteristics [1,2,3,6,11,16]. However, it may be difficult to classify into one of subtypes in these patients. Etiologically, it has been known that cortical dysplasia is caused by disorder of neuronal proliferation and/or migration [3,4,6,10,14,15,17], whereas polymicrogyria can occur from cortical damage such as cerebral ischemia in early postnatal period [16]. As microdysgenesis, which is identified only as microscopically abnormal structures of cortex, can not find in MR images, it seems to be better that cortical dysplasia is classified histopathologically. However, radiological classification is more useful clinically. Barkovich et al. [2] advocated a classification of cortical malformations. It was based on three embryological events of cortical formation; (1) neuroblast proliferation in the germinal matrix, (2) neuronal migration, and (3) neuronal organization within the cortex. Our case had abnormal gyration of polymicrogyria and macrogyria, and schizencephaly. A characteristic structure, reverse of the gray and white matter, was found in the macrogyria. Residual glial fibers might produce the superficial white matter following disturbance of neuronal migration. This white matter might prevent normal gyration and produce macrogyria. Schizencephaly may be due to disorder of neuronal proliferation in the germinal matrix. Accordingly, both disorders of neuronal proliferation and migration in early prenatal period were a possible cause of the cortical malformation in our patient. This widespread cortical malformation corresponded well to a subtype, macrogyria/polymicrogyria with neuronal cleft, in the classification of Raymond et al. [16]. However, we could not found the previous report about the reverse of the gray and white matter.

In our case, the epileptic focus on the scalp EEG was identified in the macrogyric lesion on MR images, but the focal ictal onset was not detected. The hyperperfusion area on ictal SPECT was also well correlated with the radiographic lesion. However, Intraoperative ECoG showed the epileptic activity in the neighboring polymicrogyria, not in the macrogyric lesion. There was a discrepancy between the findings of ECoG and neuroimaging. It might be explained from the histological finding that the macrogyria was covered and separated with the glial bundles. We speculated a process that the epileptic activity could be produced in both the macrogyria and polymicrogyria, but the activity from the cortical islands in the macrogyria could not conduct to the neighborhood cortical areas due to the abnormal glial bundles. However, the proper reason remained unclear.

In regard to the surgical treatment, functional hemispherectomy could be applied to the diffuse unilateral cortical dysplasia. In our case, as she was an elder child and had only hemianopsia, hemispherectomy would produce severe deficits. Avoiding the postoperative deficits, lesionectomy and/or additional MST might be the best procedure. Because the efficacy of MST alone might not suppressed seizure enough, epileptogenic zone should be resected completely as possible. The image-guided system was available to identify the eloquent areas and to perform less invasive surgery. Intraoperative ECoG was also useful to detect the epileptogenic zone.

In conclusion, surgical indication for epilepsy children with mental retardation is often hesitated, but we stress that some patients can take excellent outcome following the surgery.

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Figure Legends

Fig. 1: Preoperative T1-weighted MR images

A: serial axial images, B: 3D-reconstructed image (right posterolateral view)

A cerebral cleft in the right occipital lobe extended to the posterior horn of the lateral ventricle. A thick gray-matter intensity could be seen in the cortical area adjacent to the cleft. It showed macrogyria, and which was covered with thin layer of white matter intensity. The abnormal gray matter continued to the right thalamus and hypothalamus. Diffuse polymicrogyria was shown in the right temporo-parietal lobes. The sylvian fissure and central sulcus showed a wide and deep fissure, which surface showed polymicrogyria. These abnormal structures were well recognizable on 3D-reconstructed image.

Fig. 2: Interictal and ictal SPECT images using ^{99m}Tc-ECD

The macrogyric lesion in the occipital and posterior temporal lobes showed normal perfusion as neocortex at interictal period (a: arrow heads), and then it demonstrated marked high perfusion in ictal image (b: arrow heads).

Fig. 3: Photographs of operative field

The occipital cleft communicated to the lateral ventricle (arrow), and there was a macro- or agyric lesion, which showed yellowish-white surface (asterisk). Other exploring cortical areas showed widely polymicrogyria.

Fig. 4: Intraoperative electrocorticogram

1-20: channels of a grid electrode on the polymicrogyric cortex

S1-4: channels of a strip electrode on the macrogyric cortex

Multiple spikes were elicited from polymicrogyric area, but not found in macrogyric lesion.

Fig. 5: Photomicrographs of surgical specimens

A, B: H-E and luxol fast blue staining

Subpial gliosis (A: arrows) was observed at the surface of macrogyria, which continued to the white matter. The glial bundles separated the gray matter to cortical islands (A, B: astarisks). Original magnification = x 20

C: Immunohistochemical staining for the glial fibril acidic protein (GFAP)

Subpial gliosis was mildly positive for GFAP (arrows). Original magnification = x 20

D: Nissl's staining

There were lots of neurons, and its polarity was out of order in the cortical islands. Multipolar and floating neurons was appeared. Original magnification = x 100