Unexpected outcome (positive or negative) including adverse drug reactions

Malformations of cortical development with good clinical outcome: a case report and review of literature

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Summary

Malformations of cortical development (MCD) are important causes of chronic epilepsy. MCD encompass many varied disorders with diverse clinical manifestations. Schizencephaly, one of the MCD, is known to be complicated by various types of epilepsy, most of which are intractable. We treated a 28-year-old man with epilepsy, characterised by unprovoked generalised tonic-clonic seizures accompanied by MCD. Brain MRI detected multiple malformations including septum pellucidum defect, partial corpus callosum defect, schizencephaly, right hippocampal atrophy, cerebellar atrophy and cerebellum atrophy. 99m Tc-ethylcysteinate dimer single photon emission CT showed decreased cerebral blood flow (CBF), and the morphology of CBF defects overlapped with the anomalous findings on MRI. The clinical outcome of the patient was good despite his severe brain malformations. Although the reason of this discrepancy is unclear, the outcomes of social function and epileptic seizures may be relatively good despite severe MCD in some patients.

BACKGROUND

Malformations of cortical development (MCD) encompass varied disorders with diverse clinical manifestations and are known to be complicated by various types of epilepsy, most of which are intractable. However, we encounter a case whose clinical outcome was good despite radiological findings showing severe malformations; patient attended a general class in school, only moderate learning disabilities was noted, seizures have been controlled by anticonvulsive monotherapy with diazepam. Although this might be rare, and the reason of this discrepancy is unclear, we thought it is noteworthy to report the clinical course of this patient, that the outcome of social function and epileptic seizures can be disproportionately good despite severe MCD in some patients.

CASE PRESENTATION

A 28-year-old man presented with acute onset of dermatitis. The patient was admitted to our hospital on emergency. With regard to birth history, he was born after an uncomplicated pregnancy by caesarean section at term, with a birth weight of 3300 g and no sign of asphyxia. However, he had delayed developmental milestones, and was subsequently found to have learning disabilities. The patient was diagnosed with epilepsy at the age of 21, manifesting complex partial seizures evolving into secondary generalised seizures.

On admission, the patient appeared normal on neurological examination. Cardiac and abdominal findings were unremarkable. Physical examination showed clinodactyly of bilateral fifth fingers but was otherwise unremarkable. The Suzuki-Binet intelligence test, which is a Japanese modified version of Binet intelligence test made by the Japanese psychologist Harutaro Suzuki (1875–1966) whose examination is made of special educational and cultural considerations for children and young adult with various learning

difficulties,¹ yielded scores in the moderate learning disabilities range, with a full IQ score of 42. EEG showed small spiky waves in the right frontal region, and the background activity was dominated by 3–4 Hz slow waves (figure 1). MRI of the brain revealed multiple malformations: partial absence of the posterior septum pellucidum, partial defect of isthmus of the corpus callosum, gyral malformation, anomalous internal cerebral veins, mergence of lateral ventricle and cerebellar atrophy (figure 2).

Although optic nerve malformation is a well-known complication of partial defect of septum pellucidum,² a dilated fundus examination and visual field screening test were normal and his visual acuity was 20/40 bilaterally. The patient was able to communicate in simple phrases. 99m Tc-ethylcysteinate dimer single photon emission CT showed decreased cerebral blood flow (CBF), and the regions of CBF defects overlapped with the regions of schizencephaly depicted on MRI (figure 3). Magnetoencephalography was unremarkable. No chromosomal abnormality was detected. Despite severe multiple brain anomalies, the patient's functional ability was fair, to the extent that he was able to feed and dress himself.

By switching antiepileptic medication from carbamazepine to diazepam, his dermatitis was gradually resolved. At the latest follow-up at 28 years of age, he was seizure-free while on diazepam alone.

INVESTIGATIONS

- ▶ EEG: Small spiky waves in the right frontal region, and the background activity was dominated by 3–4 Hz slow waves.
- ▶ Brain x-ray CT/brain MRI: Multiple malformations; partial absence of the posterior septum pellucidum, partial defect of isthmus of the corpus callosum, gyral malformation, anomalous internal cerebral veins, mergence of lateral ventricle and cerebellar atrophy.

Figure 1 EEG shows sharp and waves dominated in the right frontal region.

- ▶ 99m Tc-ethylcysteinate dimer single photon emission CT: Decreased cerebral blood flow (CBF), and the regions of CBF defects overlapped with the regions of schizencephaly depicted on MRI.
- ▶ Magnetoencephalography: Unremarkable.

DISCUSSION

According to an old survey, the estimated incidence of anomaly of the central nervous system is 1.02 per 1000 births in Japan.³ In the UK, the data extracted from six regional congenital anomaly registers in England and Wales, 38 cases of schizencephaly were identified in 25 67 165 livebirths and stillbirths, giving a total prevalence of 1.48/100 000 births (95% CI 1.01 to 1.95).⁴ Some structural brain anomalies are associated with functional disturbance of the central nervous system and may impair activities of daily living.

Schizencephaly is one of the brain anomalies. In 1946, Yakovlev and Wadsworth^{5 6} investigated autopsied individuals with congenital clefts in the cerebral hemisphere, and defined schizencephaly. The anatomical feature is the presence of symmetric clefts near the central sulcus. Grey matter of the lesion is thick and histologically rich in neurons. The condition is a congenital dysplasia caused by impaired neuronal migration at around 6–7 months of embryonic age. Clinically, severe learning disabilities, hemiplegia, quadriplegia and intractable epilepsy coexist in many cases. On the other hand, some patients are reported to achieve good social function and epilepsy outcomes despite severe anomalies.

Advances in neuroimaging technology and genetic analyses have led to a significant increase in our

understanding of MCD, which has in turn enriched our knowledge of normal brain development and function as well as epileptogenesis. According to published study, focal cortical dysplasia (FCD) that includes schizencephaly is perhaps the most common MCD in MRI-based series.⁷ Epilepsy caused by FCD is commonly refractory to drug treatment. FCD is indeed an important cause of focal motor status epilepticus or epilepsia partialis continua, which may be life threatening.

However, most of the published series were reported by institutions with interests in refractory epilepsy and epilepsy surgery. Therefore, the reported prevalence of MCD in patients with epilepsy might be biased by selection and reporting; the true prevalence remains unknown.

Schizencephaly, which was previously unclassified, is currently grouped under FCD and polymicrogyria among the MCD. It is defined by the presence of a transcortical cleft, open or closed, lined by cortex, and often with polymicrogyria along the cleft borders. Clefts may be unilateral or bilateral and associated with other malformations; for example, in the septum, optic nerve, corpus callosum or hippocampus. Surgical treatment of refractory epilepsy associated with schizencephaly has been reported, but is rarely considered and not appropriate in most cases.⁸ The aetiologies are poorly understood but may be genetic, infective or hypoxic, which is probably associated with poor cerebral perfusion. Regarding the genetic mechanism, Brunelli *et al*⁹ identified heterozygous mutation in the homeobox gene, EMX2, in seven sporadic cases by gene analysis. In our patient, no genetic abnormalities were detected and there was no apparent genetic cause in the mother. Identification of the cause was not possible.

Figure 2 Coronal (A) and sagittal (B) view of MRI of the brain reveals multiple malformations: partial absence in the posterior part of the septum pellucidum, partial defect of isthmus of the corpus callosum, gyral malformation, anomalous internal cerebral veins, mergence of lateral ventricle and cerebellar atrophy. Black arrow: the partial defect of the corpus callosum. White arrow: Probst's bundle, that is, the longitudinal rest of the corpus callosum. Asterisk: the merged lateral ventricle. Arrowhead: schizencephaly.

Figure 3 99 m Tc-ethylcysteinate dimer single photon emission CT shows a decreased cerebral blood flow, and a defect is noted in a consistent shape of schizencephaly with the MRI findings (arrowhead).

The clinical manifestations of schizencephaly depend on the location and extent of the abnormalities. The clinical picture is complicated by various types of epileptic seizures such as simple partial seizure, complex partial seizure, secondary generalised seizure, febrile convulsion, generalised tonic-clonic seizure, myoclonic partial seizure and infantile spasm. Epileptogenicity in schizencephaly varies among cases. The incidence of seizures in schizencephaly is high, occurring in more than half of the cases.¹⁰ The clinical course of epilepsy in schizencephaly is often intractable in many cases.

We encountered a patient with schizencephaly, whose clinical outcome was relatively good despite severe multiple brain malformations depicted on neuroimaging studies. It is noteworthy to report the clinical course of this patient, which is disproportionally good compared to the anatomical anomalies. This case may encourage many patients who are in despair over their brain anomalies.

Learning points

- ▶ Three structural brain abnormalities can be increasingly recognised in patients suffering from intractable focal epilepsies using high-resolution imaging techniques.
- ▶ Malformations of cortical development (MCD) are responsible for many cases of refractory epilepsy in adults and children.
- ▶ Some patients with MCD, whose clinical outcome was relatively good despite severe multiple brain malformations depicted on neuroimaging studies.
- ▶ Different types of MCD have different sequelae and much of the difference may indicate the complex underlying biology of MCD.
- ▶ Although epilepsy surgery has become a successful treatment option for many patients with brain anomaly, careful presurgical evaluation for epilepsy with MCD may be essential.

Contributors The four authors are justifiably credited with authorship, according to the authorship criteria. In detail: conception, design, analysis and interpretation of data, drafting of the manuscript, final approval given.

Competing interests None.

Patient consent Obtained.

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