다양한 유형의 발작을 보인 1p36 결실증후군 1례

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1p36 Deletion syndrome Presenting with Various Epileptic Semiologies

1p36 deletion syndrome is the most common telomeric microdeletion syndrome. It is related to various clinical features including neurodevelopmental impairment, seizure, growth retardation, and heart defects. It is also known to have several morphologic features, including deep-set eyes, flat nasal bridge, straight eyebrows and pointed chin. Seizure is common in 1p36 deletion syndrome and its type and natural course is variable. Control of seizure with antiepileptic drugs is variable; however, seizure improves with time in majority of cases. We report a patient presenting with various types of seizure, developmental delay, and morphological abnormality. The patient developed complex partial seizure, infantile spasm, and myoclonic seizure, at the age of 1, 4, and 12 months, respectively. The patient was diagnosed as 1p36 deletion syndrome using array comparative genomic hybridization. At the age of 15 months, seizure disappeared and development began to progress.

Key Words: Chromosome 1p36 deletion syndrome, Seizure, Microarray analysis, Comparative genomic hybridization

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Introduction

1p36 deletion syndrome is the most common microdeletion syndrome and is characterized by a variety of neurological defects, seizure, growth retardation, heart anomalies, and distinctive morphologic abnormalities^{1,2)}. In 1993, Biegel et al.³⁾ first reported a 5-month-old girl with 1p36 deletion syndrome who had growth and developmental delays, morphologic abnormality, and a heart defect. In 1997, Shapira et al.⁴⁾ delineated the common clinical characteristics of 13 patients with 1p36 deletion. Though more than 200 cases of 1p36 deletion syndrome have been reported, no case report has been published in Korea so far.

Seizure is one of the main symptoms of 1p36 deletion syndrome. Seizures of various types and clinical courses have been reported in 1p36 deletion syndrome. However, there are few reports of patients with multiple types of seizures that developed serially, such as in our case.

Here, we report a case of 1p36 deletion syndrome diagnosed by array comparative genomic hybridization (array CGH), revealing several types of seizures that

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occurred from the age of 1 month, swallowing disturbance, developmental delay, microcephaly, and morphologic abnormality.

Case Report

1-month-old boy visited our hospital for seizure developed on the day of hospital visit. Clonic seizure of the left arm occurred 6 times every 30 minutes, each lasting for 20–30 seconds. The patient was born at the gestational age of 38 weeks and 6 days, and his birth weight was 2.59 kg. There was no perinatal problem. Metabolic disease screening results were normal. The patient's mother experienced seizure once at the age of around 3 months, which was associated with fever. There was no family history of epilepsy or developmental delay. The patient's head circumference was 37 cm (10–25th percentile). He was alert, and neurological examination results were normal.

Complete blood count, serum chemistry, and electrolytes were all within normal ranges. Brain magnetic resonance imaging (MRI) showed no abnormality other than grade 1 germinal matrix hemorrhage. Electroencephalography (EEG) revealed frequent interictal spikes and polyspikes from the right or left temporal and parietal lobes (0–3 times/10 seconds) (Fig. 1A). One clinico-electrical seizure was observed, which was sustained for 17 seconds on the left frontal lobe and both sides of the centro-frontal lobe.

Phenobarbital and pyridoxine were initiated with the diagnosis of complex partial seizure. There were no more seizures after the third day of antiepileptic therapy. The patient was discharged 7 days after admission.

During hospitalization, the patient frequently experienced choking events, so he underwent a swallowing function test. Because the test revealed pulmonary aspiration due to incomplete closure of the epiglottis, the patient began nasogastric tube feeding.

At the age of 2 months, clonic seizure of the right leg occurred more than 10 times for two days. The EEG showed spikes and polyspikes on the left central area. Carbamazepine was added, and seizure did not occur afterwards for 2 months.

At the age of 4 months, the patient developed another type of seizure characterized by sudden lifting of the extremities for a few seconds. Seizure occurred in two or three clusters a day. Hypsarrhythmia was identified in the EEG (Fig. 1B). At the time, the patient showed developmental delay and could not control his head or roll over. The patient was diagnosed with infantile spasm (West syndrome) and started taking vigabatrin. Prednisolone and topiramate were added because seizure was not controlled. Infantile spasm did not improve even after this; thus, the patient began a ketogenic diet at the age of 7 months. The intensity and frequency of the seizures gradually decreased thereafter, so antiepileptic drugs were stopped, keeping only vigabatrin. Infantile spasm completely disappeared at the age of 11 months.

Fig. 1. (A) Ictal EEG showed discharges from left central areas during right motor seizure. (B) EEG showed hypsarrhythmia. (C) Generalized spike or sharp wave followed by electrodecrement was observed during myoclonic seizure.

At the age of 12 months, the patient presented a third type of seizure, which consisted of jerking of the whole body with fixed eyes or a drooping head. This occurred more than 10 times a day. VideoEEG revealed generalized spike or sharp wave discharges (Fig. 1C), indicating that the patient's symptoms were from myoclonic seizure. The patient showed global cerebral atrophy on brain MRI. Myoclonic seizure was controlled with valproate.

The patient still had swallowing disturbance and global developmental delay. He could control his head and roll over, but could not seize a rattle. In terms of language development, he could only babble. He showed social smiling, but could not perform hand-clapping. In addition, the patient manifested morphologic abnormality as microcephaly (below 3rd percentile), sunken eyes, and a broad nasal bridge. Routine chromosomal analysis results were normal, but array CGH identified 1p36 microdeletion (Fig. 2).

At the age of 15 months, myoclonic seizure disappeared and development began to progress. The patient could sit with support and reach for toys. All antiepileptic drugs were stopped at the age of 2 years, and the patient has maintained a seizure-free state.

Discussion

1p36 deletion syndrome is telomeric microdeletion of the distal short arm of chromosome 1, with an incidence of 1/5,000–

1/10,000¹⁾. 1p36 deletion syndrome is characterized by mental retardation, developmental delay, seizure, hypotonia, visual and hearing impairment, growth delay, and heart anomalies. It is also associated with distinctive morphologic features, such as microcephaly, a large anterior fontanel, brachycephaly, straight eyebrows, deeply set eyes, a broad nasal bridge, low-set ears, and a pointed chin^{1,2,4)}. Mental retardation and developmental delay are noted in 90–100% of patients with 1p36 deletion, and swallowing disturbance is found in more than 50% of individuals.

Seizure is known to occur commonly in 1p36 deletion syndrome. Seizure has been detected in 44–79% of patients with 1p36 deletion syndrome in previous studies^{1,2,4-8)}. The type of seizure reported is variable, including infantile spasm, simple and complex partial seizures, generalized tonic-clonic seizure, and absence seizure⁷⁻⁹⁾. The onset and course of seizure also varies, and most occur during infancy or childhood⁹⁾. The control of seizure with antiepileptic drugs is variable, according to previous reports. Seizure is usually well controlled by antiepileptic drugs and tends to be gradually improved, allowing complete discontinuation of anticonvulsants. However, there are some reports of patients with intractable seizure^{8,10)}.

In this paper, we reported a patient who developed various types of seizures serially. Complex partial seizure, infantile spasm, and myoclonic seizure occurred at the ages of 1 month, 3 months, and 12 months, respectively. According to a report by Battaglia et al.⁸⁾, seizure appeared in 26 of 60 patients with 1p36 deletion syndrome, and 11 of them showed multiple types of seizures. Fifteen patients experienced infantile spasm, and eight

Fig. 2. Array comparative genomic hybridization result for patient showing deletion of 1p36 (chr1:882,140-2,684,924).

of them experienced focal or generalized clonic seizure 1–7 months before the onset of infantile spasm. Similarly, there have been several reports describing patients with different types of seizures that occurred before or after infantile spasms^{9,11}. However, to our knowledge, there has been no detailed description of cases of multiple types of serially developing seizures.

Shapira et al.⁴ conducted fluorescence in situ hybridization and deoxyribonucleic acid (DNA) polymorphism analysis of 13 patients with isolated 1p36 deletion, which revealed that there is variability in deletion sizes with no common breakpoints. By analyzing 61 patients with 1p36 deletion syndrome, Heilstedt et al.⁶ identified pure terminal deletions, interstitial deletions, derivative chromosomes, and complex rearrangements. As the type and size of the deletion varies, a variety of markers is necessary for the genetic diagnosis of 1p36 deletion syndrome⁶. Microarray test is a useful method for the diagnosis of a chromosomal disorder in that it can explore whole chromosomes and detect subtle alterations, rather than target particular loci. Shaffer et al.¹² screened 1,500 individuals with mental retardation and developmental delay. Chromosomal abnormalities were detected in 84 cases (5.6%), and eight (10%) of those turned out to be 1p36 rearrangement. In our case, 1p36 deletion syndrome was diagnosed using array CGH, although the result of conventional karyotyping was normal.

Although the specific genes that cause seizure in 1p36 deletion syndrome are not known exactly so far, two genes, KCNAB2 (voltage-gated potassium channel β -subunit gene) and GABRD (human γ -aminobutyric acid A receptor delta-subunit gene), have been assumed to be causative genes of seizure^{13,14}.

The loss of KCNAB2 results in the reduction of potassium channel-mediated membrane repolarization and therefore increases neuronal excitability. In a study by Heilstedt et al.¹³, epilepsy occurred in 89% of patients with deletion involving KCNAB2, while only 27% of patients without KCNAB2 deletion had epilepsy. However, subsequent studies conducted by Kurosawa et al.¹⁰ have not shown consistent results. Among 11 patients with 1p36 deletion syndrome, two showed intractable epilepsy, even though they did not have KCNAB2 deletion. In contrast, one patient, who had KCNAB2 deletion, had not developed epilepsy. Therefore, KCNAB2 does not seem to be the sole determinant of seizure in 1p36 deletion syndrome, and it is presumed to have a role in combination with other genes.

GABRD has been proposed as a causative gene for neurological complications in 1p36 deletion syndrome, because it is associated with the GABA channel, the primary inhibitory neurotransmitter in the brain¹⁴. In a study by Rosenfeld et al.¹⁵, three of five patients had deletions involving GABRD, and seizure

occurred in two of these. Two other patients who did not have GABRD deletions did not develop seizure.

In our case, the patient's deletion included GABRD, but KCNAB2 was not deleted. Further studies of phenotype-genotype correlation will be required in order to uncover the specific gene that induces seizure in 1p36 gene deletion syndrome.

요약

본 저자들은 생후 1개월부터 발생한 여러 유형의 발작, 삼킴장애, 발달지연, 소두증 및 형태학적 이상을 보인 남아에서 비교유전체 분석(array comparative genomic hybridization)을 통하여 1p36 결실증후군을 진단한 예를 경험하였기에 보고하는 바이다.

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