Case Report

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Diagnostic distal 16p11.2 deletion in a preterm infant with facial dysmorphism

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The 16p11.2 microdeletion has been reported in patients with developmental delays and intellectual disability. The distal 220-kb deletion in 16p11.2 is associated with developmental delay, autism spectrum disorder, epilepsy, and obesity at a young age. We have reported a case of distal 16p11.2 deletion syndrome in a preterm infant with unusual facial morphology and congenital heart disease. We suggest using chromosome microarray analysis to detect chromosomal abnormalities in newborns, especially preterm infants with unusual morphologies.

Key words: Microarray analysis, Gene deletion, Premature birth.

Introduction

The 16p11.2 microdeletion has been found in patients with the autism spectrum disorder and was described by Barnby et al. [1]. The deficient genes play important roles in neural development associated with behavior and learning and cause behavioral problems, intellectual disability, and the autism spectrum disorder [2]. The distal 16p11.2 microdeletion syndrome is associated with developmental delay, autism, seizures, and obesity, all of which occur at a young age when a 220-kb deletion is detected distal to 16p11.2 [3]. We have reported a case of the distal 16p11.2 microdeletion syndrome diagnosed in a premature infant with a dysmorphic face.

Case

A female neonate was delivered by emergency cesarean section because of premature rupture of membranes and labor. She had a gestational age of 31 weeks and five days, birth weight of 2,095 g (75th to 90th percentile), length of 44 cm (50th to 75th percentile), and head circumference of 32.7 cm (75th to 90th percentile). Her Apgar score was 5 points at one minute and 8 points at 5 minutes. The mother's age was 35 years, and she had no history of underlying disease or drug use. The infant was admitted to the neonatal intensive care unit after immediate tracheal intubation in the operating room because of respiratory distress after birth, and was diagnosed to have the respiratory distress syndrome (RDS). The chest X-ray film showed neonatal RDS, and a pulmonary surfactant was administered through the endotracheal tube. Physical examination at birth showed abnormal facial features (Fig. 1), with relative macrocephaly, a prominent forehead, edema around the eyes and lips, low-set ears, low nasal bridge, and micrognathia. She had normal muscle tone and no feeding problems at 3 days after extubation. A lumbar dimple was observed, and spinal ultrasonography was performed to check for comorbid anomalies; however, no specific results were obtained. The patient was assessed for congenital infections using the toxoplasmosis, syphilis, rubella,

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Fig. 1. Facial features and lumbar dimple. (A) Image of the face with relative macrocephaly, a prominent forehead, edema around the eyes, and low nasal bridge. (B) Sacral dimple.

cytomegalovirus, herpes screen, and all of the results were negative. The results of simple chest radiography showed that the cardiothoracic ratio was consistently above 0.6 and cardiomegaly was confirmed. Cardiological investigation revealed an atrial septal defect and a perimembranous inlet extension ventricular septal defect (VSD) at 7 days of age. Although the forehead was protruded, no morphological abnormalities of the skull were detected. Electroencephalography (EEG) was performed to confirm electronic epilepsy because the incidence of seizures is high in patients with 16p11.2 deletions. EEG findings showed immature waves on both sides of the central temporal lobe, but no epileptiform discharge. No seizures were observed during admission. Results of the neurological investigations, including EEG and brain ultrasonography, showed no abnormalities.

The patient's blood sample was sent to the Green Cross Medical Foundation on the 5th day after birth. A microarray-based comparative genomic hybridization (CGH) test was performed using the Affymetrix Cytoscan 750K array (array CGH; Thermo Fisher Scientific, Waltham, MA, USA), and a deletion of approximately 246 kb was observed in the 16p11.2 region of the chromosome (28,786,703-29,032,280)×1 (Fig. 2). After respiratory treatment, the overall muscle tone was normal, and bottle-feeding proceeded smoothly. The vital signs remained stable, and she was discharged on the 34th day (corrected age: 36 weeks and 3 days).

The patient's brother was 5 years old at that time and his face appeared similar to the patient. His chromosomal karyotyping was normal, but a microarray test was not performed. Echocardiography revealed a small secundum atrial septal defect and perimembranous VSD with an aneurysm. He had a language

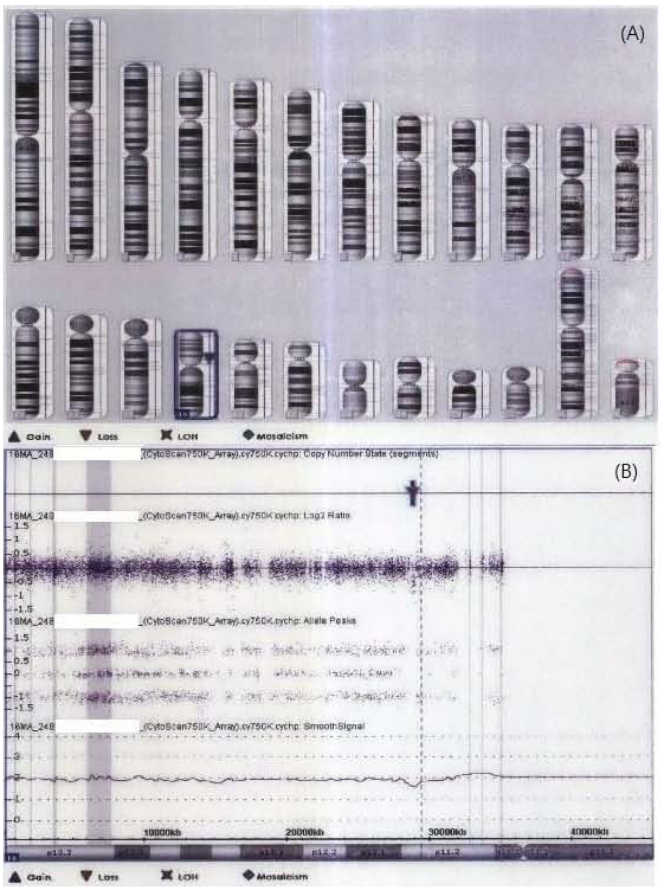

Fig. 2. Chromosomal microarray report. (A) Distal deletion of the short arm of chromosome 16. (B) A 246-kb deletion on the distal short arm of chromosome 16p11.2. Inverted triangle at chromosome 16 indicates a break point.

disorder and behavior problems that are associated with autism. We suspected that he had the same 16p11.2 deletion as his sister, but a microarray test was not performed because the parents refused to consent.

Discussion

Here, we show that dysmorphic facial appearance as the first sign of distal 16p11.2 microdeletion enables early diagnosis in a preterm infant, and congenital heart disease may occur as a malformation. The chromosome 16p microdeletion syndrome is associated with cognitive and developmental delays, behavioral disorders, and unusual facial deformities due to the deletion of the proximal short arm of the chromosome, resulting in various systemic symptoms due to gene loss [4]. Language and behavioral abnormalities, such as hyperactivity and autism, are general phenotypic characteristics of the 16p11.2 microdeletion syndrome. Therefore, the syndrome can be diagnosed at an age when an infant is exhibiting a delay in speech and development (Table 1) [4-6]. In addition, there are few reports of congenital anomalies associated with the 16p chromosome; although, congenital malformations with terminal and interstitial deletion of the long arm of chromosome 16 are well known [7,8]. Thus, we performed chromosomal microarray as the first step in the genetic diagnosis, as this method may be appropriate for patients with facial dysmorphisms or congenital abnormalities [4,9,10]. Conventional chromosomal techniques cannot be used to detect chromosomal anomalies [10], chromosome breakage, or missing materials. The microarray method allows the identification of missing fragments and chromosomal aberrations with sensitive molecular techniques and has a much higher diagnostic rate than karyotype analysis in patients with intellectual disability or congenital anomalies [10]. Developmental delay, intellectual disability, and/or autism spectrum disorder are generally the first presentations or suspected signs of 16p11.2 microdeletion [6,11] (Table 1). Many studies have reported specific facial appearance in patients with 16p11.2 deletions [4,12]. Our case shows that meticulous observation of the face for early diagnosis is needed to confirm a genetic disorder or exclude another birth defect by ruling out a microdeletion, even in premature infants.

Developmental delay, autism spectrum disorder, epilepsy, and obesity can be observed in patients with the distal 16p11.2 deletion syndrome (246-kb deletion) [3]. In our patient, the findings were induced by deletion from 28,786,703 to 29,032,280 in 16p11.2, and involved nine OMIM genes (*ATXN2L*, *ATP2A1*, *CD19*, *LAT*, *NFATC2IP*, *RABEP2*, *SH2B1*, *SPNS1*, and *TUFM*; Table 2). *SH2B1*, located at 28.73 to 28.95 Mb, is probably involved in the weight gain and obesity observed in half of the children and adults with 16p11.2 microdeletion [13]. In our case, the birth weight of the infant was in the 75th to 90th percentile, and her discharge weight was 3,050 g, which corresponds to the 75th

Table 1. Clinical characteristics in children with 16p11.2 microdeletion

Characteristic	Bijlsma et al. (2009) Case No. 15 [4]	Bamonte (2015) [5]	Tardivo et al. (2017) Case No. 1 [6]	Present case
Deletion of chromosome 16p11.2	205 kb (28.74-28.95 Mb)	-	29,674,336-30,199,351	246 kb (28,786,703-29,032,280)
Gestational age	Full term	32 weeks	Full term	31 weeks and five days
Birth weight (g)	3,750	1,758	3,120	2,095
Sex	Male	Male	Male	Female
Age at diagnosis	5 yr	7 mon	6 yr	5 day
Presentation at diagnosis	Intellectual disability	Developmental delay	Intellectual disability	Dysmorphic face
Craniofacial	Long, narrow face, prominent forehead, downslanted and narrow palpebral fissures	Gross brain edema	Hirsute forehead, straight nose, broad bridge, hypodontia, prominent chin	Prominent forehead, edema around eyes and lips, low nasal bridge, micrognathia
Ears	Fleshy earlobes	-	Dysplastic and unfolded ears	Low-set ears
Cardiac problems	-	Congenital heart murmur at 4 months	No	ASD, VSD
Feeding difficulties	-	Yes	No	No
Hypotonia	Yes	Hypertonicity	No	No
Seizure	-	Yes	No	No
Others	Risperdal medication	-	-	Dimple

-, unknown; ASD, atrial septal defect; VSD, ventricular septal defect.

Table 2. Phenotype associated with OMIM genes according to cytogenetic location of 16p11.2

Gene	OMIM No.	Chromosome position	Phenotype (if known)
Present case (16:28,786,703–29,032,280)			
ATXN2L	607931	16:28,823,047-28,837,236	Unknown
ATP2A1	108730	16:28,878,487-28,904,508	Brody myopathy (disorder of skeletal muscle function)
CD19	107265	16:28,931,734-28,939,346	Immunodeficiency
LAT	602354	16:28,984,825-28,990,782	Immunodeficiency
NFATC2IP	614525	16:28,950,991-28,966,464	Unknown
RABEP2	611869	16:28,904,420-28,925,210	Unknown
SH2B1	608937	16:28,846,599-28,874,212	Obesity, developmental delay
SPNS1	612583	16:28,973,998-28,984,768	Unknown
TUFM	602389	16:28,842,410-28,859,561	Combined oxidative phosphorylation deficiency

percentile for gestational age of 36 weeks and 3 days. The microarray analysis identified the missing base pairs in *SH2B1*. Therefore, continuous obesity monitoring and nutritional follow-up are required. In addition, this neonate should be observed for delays in language expression, which are the first signs of developmental delay, especially in infants who do not babble or speak at infancy. Neurology and psychopathology follow-up are recommended to observe for signs of autism and intellectual disabilities [6]. CD19 is a cell surface molecule expressed in hematopoietic B lymphocytes and follicular dendritic cells [11]. Mutations/deletions in *CD19* cause immunodeficiency and deletion of the contiguous LAT region increases susceptibility to infections (Table 2). Although cardiac defects have been reported with a typical 16p11.2 deletion or 16p11.2 - p12.2 microdeletion syndrome [11], patients with a distal 16p11.2 microdeletion did not reveal any heart abnormalities [3]. TUFM is an alternative name for mitochondrial translation elongation factor Tu (EF-Tu) [14]. Smeitink et al. [14] revealed that fatal hypertrophic cardiomyopathy occurred when mitochondrial elongation factors, such as guanine nucleotide exchange factor of EF-Tu, were mutated. However, four genes (*ATP2A1*, *CD19*, *LAT*, and *TUFM*) deleted in our patient are autosomal recessive, and our findings were not consistent with the phenotype of this cardiomyopathy and infection such as otitis media. In addition, chromosomal microarray cannot detect balanced translocations, low-level mosaicisms, inversions, and point mutations [10]. Thus, it is important to search for the gene associated with the congenital heart problem as well as explain the genotype-phenotype relationship of unknown genes. In addition, patients with the distal 16p11.2 microdeletion syndrome should be monitored to determine whether new clinical expressions appear, taking into account differences from previous patients with 16p11.2 deletion.

We interviewed the parents to determine whether their appearance exhibited new or inherited micro-defect patterns that could be propagated in an autosomal dominant pattern [12]. The parents of our patient did not exhibit abnormal behaviors such as autism, language communication, and morphological abnormalities. However, the patient's older brother showed symptoms of suspected autism and language delay, and his face at birth was reportedly similar to that of his younger sister. However, a microdeletion could not be detected by conventional chromosomal analysis, and the result was 46,XY(22pstk+). Further tests, such as a microarray test, were recommended, but the parents refused. The parents should undergo karyotyping and appropriate genetic counseling before another pregnancy because parents with balanced translocation are more likely to have children with chromosomal abnormalities, such as deletions. An additional limitation was that we did not use a targeted surveillance such as fluorescence *in situ* hybridization to confirm inherited or *de novo* development [10].

The 16p11.2 microdeletion cannot be detected with conventional cytogenetic karyotyping. We detected this microdeletion in a premature infant with abnormal facial features using a microarray test, rather than karyotyping. In addition, microarray testing is required for not only the early diagnosis of such genetic diseases, but also additional obstetric genetic counseling for premature infants. In Korea, the microarray method is not yet covered by health insurance, and the cost is high. However, many researchers have reported the clinical utility of the microarray method. In some neonates with incomplete symptoms, the chromosomal microarray method may be a useful tool for early diagnosis.

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