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Clinical characterization of a Korean case with 3p25 deletion

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Chromosome 3 (3p) deletion syndrome is a rare genomic disorder caused by a deletion at the terminal end of the short arm of chromosome 3. The primary characteristics of the syndrome are delayed development, dysmorphic features, and several other congenital anomalies. Here, we describe the case of a 2-year-old Korean girl with typical features of 3p deletion syndrome, including dysmorphic facial features, low birth weight, developmental delay, growth and cognitive retardation, and congenital heart disease. This case represents the first report of 3p deletion syndrome in Korea. Although phenotypes can be variable among patients, a clinically recognizable pattern has been described for this genetic defect, and our report helps to identify other cases with 3p deletion syndrome from a clinical and genetic perspective.

Key words: Chromosome 3, Congenital abnormalities, Intellectual disability.

Introduction

Genomic alterations in the telomeric region of the short arm of chromosome 3 (3p) are associated with two major syndromes: 3p deletion and 3p trisomy syndrome [1,2]. Both syndromes are clinically characterized by various types of dysmorphisms and mental or cognitive retardation [2].

Deletions of this genomic portion develop sporadically in most cases, and the major break-points are mapped to chromosome 3p25 [3]. The most common characteristics of 3p deletion syndrome include low birth weight, hypotonia, mental retardation, developmental delay, and dysmorphic features such as microcephaly, ptosis, hypertelorism, and micrognathia [4].

However, some phenotypes vary among patients, such as developmental delay, which can range from mild to severe. In addition, some clinical manifestations of 3p deletion syndrome show phenotypic similarities with other genetic diseases, making it difficult to accurately diagnose the syndrome in some cases.

To date, only 3 cases of 3p trisomy with congenital anomalies have been reported in Korea [5-7], and there have been no reports of patients with 3p deletion syndrome, suggesting the rare incidence as well as under-recognition of this syndrome. In this report, we describe the case of a child with the typical features of *de novo* 3p deletion syndrome resulting from partial monosomy for the distal part of the short arm of chromosome 3.

Case

The patient was born at 37 weeks of gestation via emergent cesarean section due to remarkably decreased fetal activity. She was the first child born to parents of a non-consanguineous marriage. There was no family history of congenital anomalies or developmental delay. The patient's birth length, weight, and head

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circumference were 75 cm (10th-50th percentile), 2,420g (3rd-10th percentile), and 32 cm (10th-50th percentile), respectively.

Craniofacial dysmorphic features included sparse hair, a round face, hypertelorism, bilateral ptosis, epicanthal folds, narrow palpebral fissures, poorly formed ear auricles, a flat nasal root, a short neck, and an abundant nape. Initial ophthalmologic and auditory screenings based on an automated auditory brainstem response test were normal. However, mild conductive hearing difficulty was observed following recurrent otitis media from the age of two months. The follow-up examination showed decreased auditory evoked potentials in both ears at the age of 20 months. A grade 2/6 systolic ejection type cardiac murmur was audible on the left sternal border, and a 2.5-2.8-mm patent ductus arteriosus (PDA) and a small secundum atrial septal defect (ASD) were observed on the echocardiogram. Device closure was performed to treat the PDA at the age of 21 months. There was a small sacral dimple and the findings of the spinal ultrasound exam were normal. Hyperthyrotropinemia was found during newborn screening, but thyroid function normalized when the patient was 1 month old. There was no kidney or gastrointestinal tract anomaly on her abdominal ultrasonography at the age of 5 months, and there were no deformities on her four extremities.

At the age of 12 months, the patient could crawl and sit with support. The Denver developmental test was performed at the age of 13 months and showed global developmental delay with a personal-social and motor developmental age of 9-10 months. At 22 months, the Bayley developmental test was performed, which also showed global developmental delay; her mental development was at a 15-month-old level and her motor development was at a 10-month-old level. At the age of 2 years, the patient developed tonic-type seizures and an electroencephalogram showed occasional sharp waves in the left parietal area, but her brain magnetic resonance image, performed at 8 months old, showed no abnormal findings. The patient has been taking an antiepileptic medication (valproic acid) to control epilepsy. Upon follow-up examination at the age of 22 months, her height was 78.1 cm (3rd-10th percentile), weight was 9.9 kg (10th percentile), and head circumference was 44.3 cm (3rd percentile).

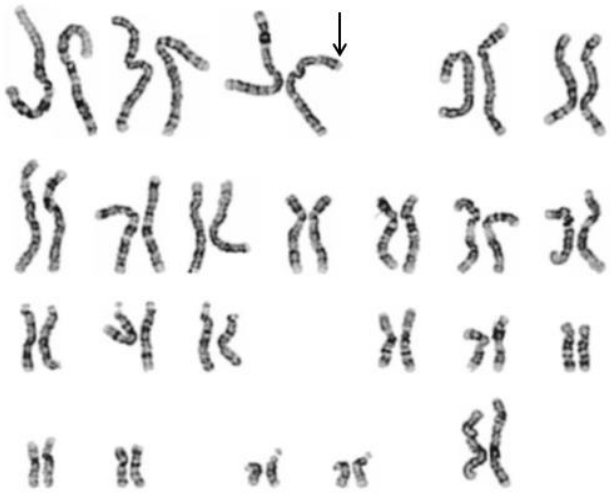

Fig. 1. The patient's karyotype: 46,XX,del(3)(p25).

The patient's karyotype, based on peripheral blood analysis, was determined to be 46, XX, del(3)(p25) (Fig. 1). Her parents showed normal karyotypes.

Discussion

This report describes the first Korean case of 3p deletion syndrome. Deletions at the terminal end of the short arm or an interstitial deletion of chromosome 3 are characterized by a recognizable phenotype such as low birth weight (52.9%), microcephaly (43.1%), hypertelorism (51.0%), ptosis (31.4%), and a varying degree of growth and mental retardation (80.4%) (Table 1 [4,8-14]). Other rare phenotypes observed are polydactyly (33.3%), sacral dimples (23.5%), cleft palate (7.8%), congenital heart defects (29.4%), and genito-urinary tract anomalies (29.4%) (Table 1 [4,8-14]). 3p25 deletion syndrome was first reported by Verjaal and De Nef in 1978 [15]. Since then, more than 50 cases of children with this condition have been described. The frequency of clinical manifestations of the previously reported 50 cases and the present case are summarized in Table 1. Although some patients with a mild phenotype have been described [16], the majority of patients with 3p deletion syndrome suffer from moderate to severe mental or cognitive impairment.

3p deletion syndrome is a rare contiguous genomic disorder resulting from the deletion of the distal end of chromosome 3p25. Deletions of 3p25 of various sizes involving several different genes have been reported demonstrating the resultant clinical phenotypes of 3p deletion syndrome [3]. Recently, Peltekova et al. [8] reported a patient with a small interstitial deletion of 643 kb who had the typical facial features of 3p deletion, growth retardation, seizures, and congenital heart disease.

There is growing evidence that haploinsufficiency of four genes at chromosome 3pter, *CHL1* (MIM*607416), *CNTN4* (MIM*607280), *CRBN* (MIM*609262), and *SRGAP3* (MIM*606525), may play an important role in the cognitive

Table 1. Frequency of clinical manifestations in 50 previous cases and in the present case of 3p deletion syndrome [4,8-14]

	Affected frequency (n)	Status in the presented case	Total (%)
Triangular face	11		21.6
Microcephaly	22		43.1
Flat occiput	10		19.6
Forehead abnormality	12		23.5
Epicanthal fold	17	+	35.3
Hypertelorism	25	+	51.0
Short palpebral fissure	11	+	23.5
Ptosis	15	+	31.4
Synophrys	12		23.5
Nose abnormality	37	+	74.5
Long philtrum	34		66.7
High arched palate	15		29.4
Cleft palate	4		7.8
Micrognathia	25		49.0
Preauricular pit	10		19.6
Low set ears	30		58.8
Ear malformation	25	+	51.0
Low birth weight	26	+	52.9
Psychomotor retardation	40	+	80.4
Growth retardation	36	+	72.5
Epilepsy	12	+	25.5
Short neck	7	+	15.7
Syndactyly	5		9.8
Clinodactyly	11		21.6
Polydactyly	17		33.3
Sacral dimple	11	+	23.5
Hypotonia	21		41.2
Congenital heart disease	14	+	29.4
Genito-urinary tract abnormality	15		29.4
Gastro-intestinal abnormality	7		13.7
Hearing impairment	11	+	23.5

impairment associated with this syndrome [2,10,17]. The *CNTN4* gene encodes a neuronal adhesion molecule that is involved in axonal growth, guidance, fasciculation, and synaptic plasticity [18]. The *CRBN* gene encodes an ATP-dependent Lon protease, which is expressed in the human hippocampus. Deletion of this gene may alter the regulation of mitochondrial energy metabolism [19]. The *CHL1* gene, belonging to the L1 family of cell adhesion molecules involved in neuronal growth and axonal guidance, is highly expressed in the cerebral cortex, thalamus, hippocampus, and amygdala [1]. Defects in *CHL1* have been suggested to cause additional detrimental effects on cognitive function [1]. SRGAP3 is particularly highly expressed in the brain, predominantly in the cerebral cortex and hippocampus, and plays an important role in higher cognitive function by regulating neuronal migration and axonal branching [20].

Approximately one third of 3p deletion syndrome patients have congenital heart defects, typically atrioventricular septal defect (AVSD), and our patient had PDA and ASD. Previous reports identified some candidate genes responsible for AVSD in 3p syndrome. The haploinsufficiency of *CAV3*, which is located within close proximity to three microsatellite markers located at 3p25 (D3S18, D3S4163, and D3S4593) and encodes carveoline-3 in cardiomyocytes and skeletal muscles, is a known factor responsible for the congenital heart defects associated with 3p deletion syndrome [9]. Mutations in this gene have been associated with several muscle disorders, such as autosomal dominant limb-girdle muscular dystrophy type 1C, as caveolin-3 protein is involved in membrane trafficking [9]. Although several of the genes located near the break point have been proposed to be associated with clinical features of 3p deletion syndrome, a causative relationship between a certain genetic defect and the presenting phenotypes remains elusive.

Parental chromosome analyses are mandatory for genetic counseling, even though most cases of 3p deletion syndrome are sporadic. The 3p deletion in our case occurred *de novo*, and the risk of recurrence in any future pregnancy is low. Because of its broad phenotypic diversity, some family members with the 3p deletion show only mild dysmorphic features [10]. Therefore, it is difficult to predict the phenotypic severity of the syndrome based only on chromosomal findings [10,16].

This study describes the first patient with 3p deletion syndrome in Korea, who presented with facial dysmorphisms, congenital heart defects, and developmental delay. Our experience should help general physicians to better understand this condition from both clinical and genetic perspectives and to facilitate identification of more cases.

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