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Del(18)(q12.2q21.1) syndrome: a case report and clinical review of the literature

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Abstract. – The terminal deletion of the long arm of chromosome 18 is relatively common among cytogenetic abnormalities, which occur incidentally in approximately 1 in 40,000 live births. Proximal interstitial deletions of the long arm of chromosome 18 are less frequent. The critical region on chromosome 18 of this syndrome is del(18)(q12.2q21.1) and has recently been recognized as a new clinical entity. We describe a 8-year-old boy with developmental delay, obesity, and epilepsy, with characteristic facial anomalies in whom G-banding chromosome analysis revealed a unique karyotype of 46, XY, del(18)(q12.2q21.1). The patient was diagnosed with interstitial deletion chromosome 18q-syndrome. He received weight control therapy from a medical dietitian. For his epilepsy, he was administered oral carbamazepine at 4 mg/kg/day. At age six, he entered a special needs elementary school. After entering school, he often showed hyperkinesis, and was diagnosed with attention deficit hyperactivity disorder with mild mental retardation. Because patients with only del(18)(q12.2q21.1) have no serious associated malformations, physicians should be aware that even adult patients may have 18q-syndrome.

Therefore, if epilepsy occurs in patients with minor facial anomalies, psychomotor retardation, obesity, and the possibility of 18q-syndrome with del(18)(q12.2q21.1) should be kept in mind, and chromosome testing should be performed.

Key Words:
18q-, 18q12.3, Interstitial deletion, Obesity, Epilepsy.

Introduction

Terminal deletion of the long arm of chromosome 18 is relatively common among cytogenetic abnormalities, which occur incidentally in approximately 1 in 40,000 live births[1]. However, proximal interstitial deletions of the long arm of chromosome 18 are less common[2-6]. The critical region on chromosome 18 for this syndrome is del(18)(q12.2q21.1) and has recently been recognized as a new clinical entity of the del(18)(q12.2q21.1) syndrome[7,8]. The interstitial deletion 18q-syndrome is clinically characterized by developmental delay, seizures, obesity, abnormal behavior, and minor facial anomalies including ptosis, bilateral epicanthus strabismus, short and slightly down-slanting palpebral fissures, full cheeks, etc[1-14]. To our best of knowledge, only seven liveborn patients with interstitial deletion restricted involving del(18)(q12.2q21.1) have been reported in the literature[2-6]. Here, we describe an 8-year-old boy with developmental delay, obesity, and epilepsy, with characteristic facial anomalies in a de novo del(18)(q12.2q21.1).

Case Report

The patient was born with a weight of 3,285 g and height of 49.5 cm. His head and chest circumference were each 33.0 cm. His mother had one previous normal delivery. Delivery at 39+ weeks gestation was difficult, and he was diagnosed with the meconium aspiration syndrome. At the time of his birth, his father and mother were 38 and 31 years of age, respectively. Although slight, mild muscle hypotonia of his extremities was observed, signs of birth asphyxia were not noted at delivery. Multiple minor facial anomalies such as ptosis, short and slightly down-slanting palpebral fissures, and moon face with full cheeks were recognized. No significant defects, including heart, lung or brain, were noted. Concerning motor movement, he was able to sit at ten months of age, and could walk while holding onto something at one year and four months of age. He could speak several meaningful words at one year and six months. Stridor was repeatedly heard from eight months, and he was diagnosed with baby asthma at 11 months. His motor development and asthma were monitored after that.

When he was three years old, his physique was revealed to be characterized by macrocephaly and obesity. His head circumference at

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the age of 2 years and 11 months was 53.5 cm (+2.56 SD). His stature and weight were 91.3 cm (-0.41 SD) and 16.0 kg (+1.5 SD), respectively (Figure 1). He was started on weight control therapy with a medical dietitian. One testicle was fixed in the intraabdominal space. For his nonpalpable testicle, surgery was performed to correct the testicular fixation at three years and four months. At that time, he could run and jump actively. His developmental intelligence quotient index was 92, and his verbal intelligence quotient index was 52; he was diagnosed with mild mental retardation. At age four years, his breathing frequently ceased for durations of more than 20 seconds during his sleep, and he was diagnosed with obstructive sleep apnea syndrome. Moreover, he experienced general tonic-clonic convulsions several times in the middle of the night with no fever. A sleep-induced electroencephalogram exhibited multifocal spikes in both hemispheres of the centro-parietal area. Brain magnetic resonance imaging (MRI) yielded normal findings. Based on these results, he was diagnosed with epilepsy and was started on oral administration of carbamazepine 4 mg/kg/day.

To explore the cause of his mild facial anomalies, obesity, infantile motor developmental delay and mild mental retardation, sleep apnea syndrome, epilepsy and other conditions, we performed several examinations. Blood and urine screening tests showed normal data. High resolution and G-banding chromosome analysis (Figure 2) using peripheral lymphocytes was performed due to his many symptoms, which re-

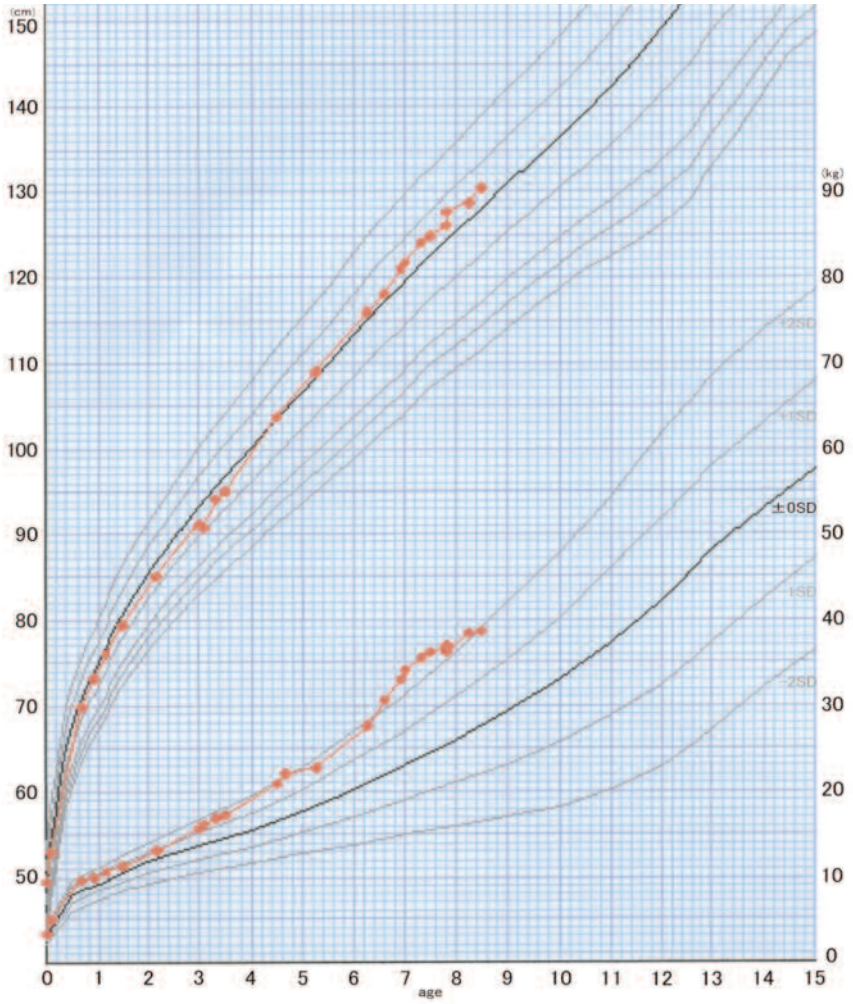

Figure 1. Cross-sectional growth chart curve with Japanese boy. The growth curve of his physique revealed over +2.0 SD obesity after 8-years-of his age.

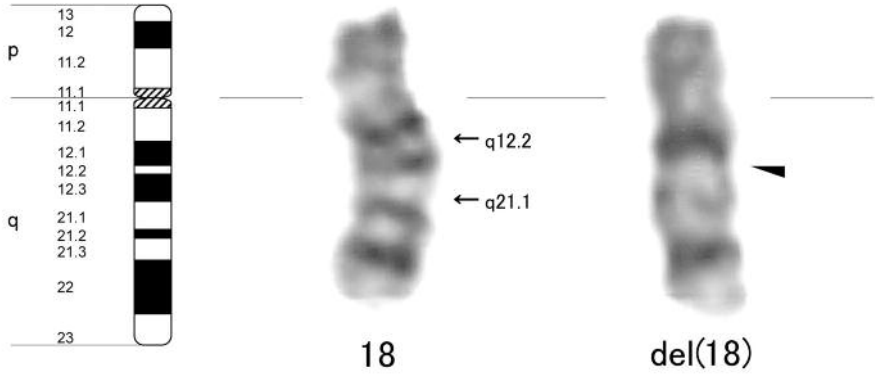

Figure 2. Chromosome analysis. G-banding metaphase chromosomes was carried out on short-term lymphocyte cultures using standard procedures. Chromosome analysis is at 850-resolution revealed 46,XY,del(18)(q12.2q21.1).

vealed a unique karyotype of 46, XY, del(18)(q12.2q21.1). Therefore, he was diagnosed with interstitial deletion chromosome 18p-syndrome. Additional chromosomal analysis by spectral karyotyping (SKY) using 24-color probes showed normal findings.

At age six years, he entered a special needs elementary school. His epilepsy and asthma were well controlled with carbamazepine and pranlukast hydrate, respectively. After entering the special needs elementary school, he often showed hyperkinesis and received a warning from his teacher that he did not listen while others were talking**.** He was diagnosed with attention deficit hyperactivity disorder with mild mental retardation. Also, he was being followed for nocturnal enuresis at eight years of age.

Discussion

Trisomy 18, 18p-syndrome, and 18q-syndrome have been established as syndromes associated with chromosome 18 abnormalities. At least 100 cases of 18q-syndrome, based on a deletion in chromosome 18, have been reported[15]. Many reports of 18q-syndrome describe a simple terminal deletion, but reciprocal translocations and a microdeletion of only 18q12.3 have also been reported[3,11,12,14]. The breakpoint is often 18q21 (OMIM#601808). Serious incomplete myelination of the brain, which is seen in many cases of 18q-syndrome, is due to an abnormality of the 18q23-*MBP* gene[9,10].

Growth hormone deficiency is associated with haplo insufficiency of the *MBP* or *GALR1* gene[16]. This is a contiguous gene syndrome with haplo insufficiency of a gene with a deleted region. Occasionally, part of a chromosome of unknown origin adheres to the 18q deleted region. In such cases, an attempt to identify the unknown region by G-band chromosome analysis of the parents, or spectral karyotyping (SKY), a special fluorescence in situ hybridization (FISH) technique with differential staining of all chromosomes is necessary[17,18].

On the other hand, interstitial deletions of the long arm of chromosome 18 are rare, and the phenotype depends on the deleted region. Among interstitial deletions, case reports of del(18)(q12.2q21.1) are increasing, and the del(18)(q12.2q21.1) syndrome is now recognized as a new clinical entity. Only seven cases of del(18)(q12.2q21.1) syndrome have been reported to our knowledge (Table I)[2-6]. Patients with even larger deleted regions, including del(18)(q12.2q21.1), have also been reported as having the del(18)(q12.2q21.1) syndrome. However, with abnormalities of the 18q23-*MBP* gene with even larger deleted regions, clinical findings, including severe mental retardation, differ depending on the deleted region. Therefore, Table I lists cases where the deleted region is limited to del(18)(q12.2q21.1)[2-6].

As shown in Table I, in 18q-syndrome, when del(18)(q12.2q21.1) is the only deleted region, common clinical features include minor facial anomalies, delayed motor and speech development, hypotonia, obesity, and epilepsy[2-6]. Moreover, 18q-syndrome, when del(18)(q12.2q21.1) is the only deleted region, is characterized by the absence of serious heart, lung, or brain complications. The oldest reported patient with 18q-syndrome involving only del(18)(q12.2q21.1) was a

Table I. Clinical features in the reviews of reported 8 cases with non-mosaic of del(18)(q12.2q21.1) syndrome.

	Tinkle BT et al (2003)[2]	Engelen JJ et al (1998)[3]	Schinzel A et al (1991, case 1)[4]	Schinzel A et al (1991, case 2)[4]	Schinzel A et al (1991, case 3)[4]	Wilson MG et al (1989)[5]	Kotzot D et al (2005)[6]	Our case (2015)
Deletion (18)	(q12.2q21.1)	(q12.2q21.1)	(q12.2q21.1)	(q12.2q21.1)	(q12.2q21.1)	(q12.2q21.1)	(q12.2q21.1)	(q12.2q21.1)
Sex	Female	Male	Female	Male	Male	Male	Female	Male
Parents age M/F	ND	ND	24/26	ND	ND	32/34	27/35	31/38
Birth								
Week	Term	Term	ND	Term	37	Term	Term	39
Length	ND	48 cm	ND	ND	50 cm	51 cm	52 cm	49.5 cm
Weight	ND	2690 g	ND	3010 g	2600 g	4600 g	2880 g	3285 g
Facial anomaly								
Strabismus	ND	+	ND	+	+	ND	+	+
Epicanathus	-	+	+	ND	+	+	+	+
Deep set eyes	+	+	ND	ND	ND	+	+	+
Abnormal behavior	+	ND	+	ND	+	+	+	+
Developmental delay	+	+	+	+	+	+	+	+
Seizures	+	+	+	+	+	+	+	+
Hypotonia	ND	+	+	+	ND	+	+	+
Last examination (y.m.)	67y	2y 8m	4y 11m	2y 5m	4y 10m	7y	1y 8m	8y 7m
Height	150 cm	95 cm	100 cm	ND	108 cm	134 cm	84 cm	131 cm
Weight	72.5 kg	15 kg	16.5 kg	18.7 kg	20 kg	59.5 kg	12.2 kg	38.5 kg

M = mother, F = father, ND = no data, y = year, m = months

67-year-old woman[2], thus indicating that long-term survival is fully possible. Epilepsy, which is seen in all cases, can be treated with conventional anti-epileptic drugs, and no intractable epilepsy has been reported and one had intractable epilepsy[13].

Because patients with only del(18)(q12.2q21.1) have no serious associated malformations, physicians should be aware that even adult patients may have 18q-syndrome. Therefore, if epilepsy occurs in patients with minor facial anomalies, psychomotor retardation, and obesity, the possibility of 18q-syndrome with del(18)(q12.2q21.1) should be kept in mind, and chromosome testing should be performed.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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