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Case report

A case of mosaic ring chromosome 13 syndrome

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= Abstract =

The clinical features of ring chromosome 13 include mental and growth retardation, CNS anomalies, facial dysmorphism, cardiac defects, genital malformations, limb anomalies, skeletal deformities and anal malformations. Although many cases of ring chromosome 13 have been reported worldwide, only 6 cases have been reported in Korea, and the latter cases were not mosaic but pure ring chromosome 13. Here we report a case with mosaic ring chromosome 13. The baby boy was born at 37 weeks of gestation by induced vaginal delivery due to intrauterine growth restriction (IUGR). He was the second baby of a 28-year-old hepatitis B carrier mother and a 32-year-old father. There was no family history of chromosomal anomalies. The baby was a symmetric IUGR with a birth weight of 1,860 g, length of 44.8 cm, and head circumference of 29.4 cm. The physical examination revealed microcephaly, trigonocephaly, flat occiput, large ears, short neck and dysmorphic facial features, including microophthalmia, hypertelorism, antimongoloid slanting palpebral fissures, a flat nasal bridge, and micrognathia. The karyotype of this patient performed by peripheral blood lymphocytes was 46,XY,r(13)(p13q34)/45,XY,-13/46,XY,dic r(13;13)(p13q34;p13q34). The baby showed failure to thrive, hypotonia, and developmental delay. We report the first case of mosaic ring chromosome 13 in a male baby in Korea and compare this case with other Korean cases of non-mosaic ring chromosome 13. **(Korean J Pediatr 2009;52:242-246)**

Key Words : Mosaicism, Ring chromosome 13, Facial dysmorphism, Intrauterine growth restriction (IUGR)

Introduction

Many cases of abnormal karyotypes involving rings of D group chromosomes have been published since the first report by Wang et al[1]. Only six cases of ring chromosome 13 have been reported in Korea[2-7] since the first report by Lee et al[2], all of these Korean reports were the cases with non mosaic ring chromosomes. A ring chromosome is formed by a break in both the long and short arms of a chromosome. The natural history of the affected patient is depend on the deleted chromosomal segments[8, 9]. The clinical features of ring 13 include CNS anomalies, facial dysmorphism, cardiac anomalies, genital malformations, limb anomalies, skeletal malformations and anal malformations[9]. One of the most significant and consistent features is the presence of facial dysmorphism. We report the first case of mosaic ring chromosome 13 in a male baby and compare the findings with other reported Korean cases of non mosaic ring chromosome 13.

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Case report

The baby was born at 37 weeks of gestation by induced vaginal delivery due to intrauterine growth restriction (IUGR). He was the second baby of a 32 year-old father and a 28 year-old mother. His elder sister was born at full- term and has no known abnormalities. The mother was a hepatitis B carrier. At approximately 28 weeks of gestation, fetal IUGR was suspected on the antenatal ultrasonography. At 36 weeks of gestation, fetal growth seem to be continuously restricted and amniotic fluid index (AFI) was decreased. The mother was transferred to our hospital one day before delivery. Baby's birth weight was 1,860 g, the length was 44.8 cm and the head circumference was 29.4 cm, all below the 10th percentile, consistent with symmetric IUGR.

The physical examination revealed microcephaly, trigonocephaly, a flat occiput and dysmorphic facial features including microophthalmia, hypertelorism, antimongoloid slanting palpebral fissures, a flat nasal bridge, micrognathia with relatively large ears and a short neck. The heart sound was normal. The anus was patent and meconium was expelled within 12 hours of birth. There was no limb, skeletal or genital anomalies (Fig. 1A-C).

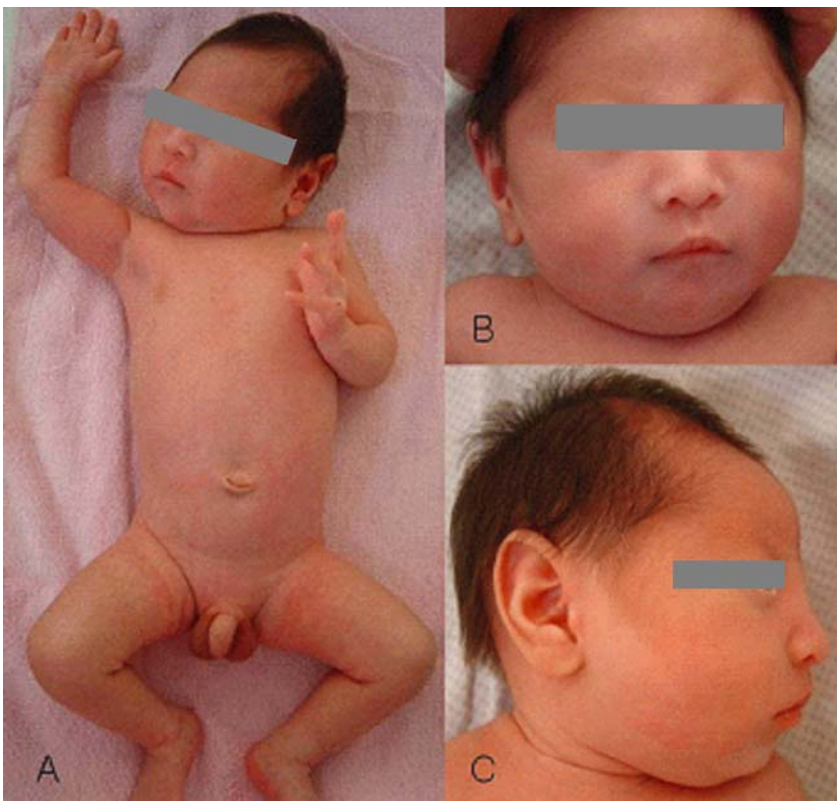

Fig. 1. Gross appearance. (A) For dull facial expression and hypotonia, (B & C) for microcephaly, trigonocephaly, hypertelorism, microophthalmia, antimongoloid slant, large ear, wide and flat nasal bridge, micrognathia and short neck.

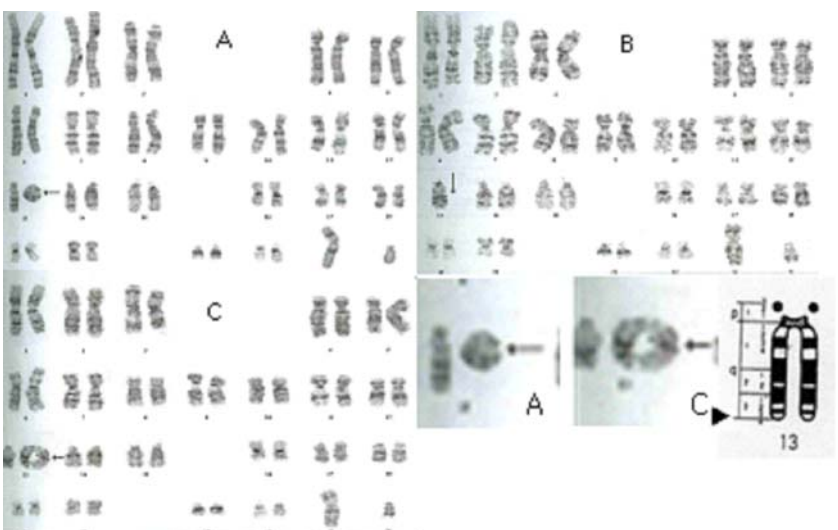

Fig. 2. Karyotypes of the patient. (A) for 46, XY, r(13)(p13q34), (B) for 45, XY, -13, (C) for 46, XY, dic r(13;13)(p13q34;p13q34).

Table 1. Comparisons of Clinical Features with Previously Reported Korean Cases

	1988[2]	1991[3]	1992[4]	1995[5]	1998[6]	2006[7]	Case
Sex	F	F	F	F (A)	F	F	M
GA (wk)	38	full-term	39	40	42	36	37
Birth weight (g)	1,920		2,600	2,100	2,000	1,560	1,860
Maternal age (yr)	29	26	27	28	21	32	28
Ring breakpoints	?	?	p11q33	?	q33	?	p13q34
Facial dysmorphism	+	+	+	+	+	+	+
Imperforated anus	+	−	−	+	?	+	−
Hand, foot anomalies	+	+	+	+	+	+	+
Heart defect	−	−	PDA	ASD, PDA	−	ASD, VSD, PDA	−
Renal defect	?	?	−	+*	?	?	−
Mental retardation	+	?	+	?	+	?	+
Brain anomaly	?	+†	?	+‡	+§	+‖	−

Abbreviations : F, female; A, ambiguous; M, male; GA, gestational age; ? no information; PDA, patent ductus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect
*both simple hypoplasia and oligomeganephronia
†posterior fossa cyst, communicating with 4th ventricle, widening of vallecula associated cerebellar hypoplasia, which is compatible with Dandy-Walker variant finding (CT)
‡large single ventricle, agenesis of both eye and optic nerve (autopsy)
§venous angioma In the right frontal lobe (MRI)
‖septum pellucidum agenesis (MRI)

The routine laboratory data showed Hb 16.4 g/dL, and WBC 5,100/mm^3 (neutrophil 35.9%, lymphocyte 50.4%, eosinophil 3.0%). The liver function tests, serum electrolytes, glucose, BUN, and creatinine were within normal range. The TORCH-IgM, and metabolic screening tests were negative. The genitourinary ultrasonography and brainstem auditory evoked potential were normal. The cranial ultrasonography showed a right prominent caudothalamic angle and grade 1 periventricular echogenicity, bilaterally. On the ophthalmologic examination, a relatively hyperpigmented iris was noted.

The baby showed hypotonia and mild respiratory distress. The baby received oxygen supply for couple of days. The baby showed jaundice on the third day of life and phototherapy was done for six days.

Because of the dysmorphic features, chromosome analysis was performed. GTG banding of peripheral blood lymphocytes revealed a mosaic karyotypes with abnormalities of chromosome 13 including monosomy, ring chromosome, and a dicentric ring chromosome, 46,XY,r(13)(p13q34)/45,XY,-13/46,XY,dic r(13;13)(p13q34;p13q34). The total number of cells counted was 50. There were 44 monocentric ring chromosomes, three monosomy 13, and three dicentric 13 ring chromosomes (Fig. 2).

At 1 year 3 months of age, the body weight of the baby was 7.5 kg, which was below the 3rd percentile. The patient had global developmental delay including motor skills, personal-social interaction and language.

Discussion

The clinical presentation of patients with ring chromosome 13 abnormalities can be various and is correlated with the extent of the deletions along chromosome 13 and the stability of the ring[10-15]. Severe phenotypes associated with large deletions of 13q have been described as the "ring chromosome 13 syndrome"[16]. A phenotype similar to the deletion 13q syndrome has been noted in patients with rings involving chromosome 13. Patients with proximal deletions that do not extend into band q32 have mild to moderate mental and growth delays with variable minor anomalies. Patients with more distal deletions including at least part of band q32 usually have severe mental and growth delays, and major malformations including microcephaly, CNS malformations, distal limb anomalies, eye defects, and gastrointestinal malformations. Patients with the most distal deletions, involving q33-q34, have severe mental retardation but usually do not have growth deficiency or gross structural malformations[17]. Our patient had two types of ring chromosome involving q34 and one monosomy with severe growth and developmental retardation, however, he did not have major structural malformations except facial dysmorphism.

Brandt et al[13] reported that efforts to fit patients into phenotypic categories on the basis of their identified ring breakpoints have not been very successful. The clinical symptoms

of patients with a ring chromosome appear to be caused by the structural chromosome deletion in addition to the specific behavior of the ring chromosome[9]. The clinical features associated with a ring chromosome 13 include growth deficiency, which usually has prenatal onset, mental deficiency, and brain malformations such as microcephaly with trigonocephaly or holoprosencephaly, as well as facial dysmorphism including a prominent nasal bridge, hypertelorism, ptosis, epicanthal folds, microophthalmia, colobomata, retinoblastoma (usually bilateral), prominent maxilla, micrognathia, prominent slanting and low set ears, and a short webbed neck. In addition, cardiac defects, hypospadias, cryptorchidism, limb anomalies such as small to absent thumbs, clinodactyly of fifth finger, fused metacarpal bones 4 and 5, talipes equinovarus, short big toe and focal lumbar agenesis have been described[18].

Cindy et al[19] classified 13q deletion into four groups; group A, a mosaic partial monosomy 13q, group B, nonmosaic rearrangements (rings or deletions) that led to a net deletion of distal 13q, group C, mosaicism for a distal 13q deletion with another cell line that is monosomic for chromosome 13, and group D, complex chromosome rearrangements that resulted in mosaicism for partial duplications and partial deletions of chromosome 13. In the group A, digital anomalies, including prominent thumb underdevelopment, abnormal face such as hypertelorism, abnormal palpebral fissures, and depressed nasal bridge, microcephaly, IUGR, and anomalies of the anus and central nervous system were present. Group B showed more severe phenotypes including anencephaly, encephalocele, and severe microcephaly. In the group C, genitourinary defects, renal defects and stillbirth were present. In group D, there was a less consistent phenotype and a higher frequency of facial dysmorphism. Our case was most consistent with the group D phenotype.

Our case showed clinical features similar to previous cases reported in Korea, such as IUGR, growth and developmental delay, facial dysmorphism including a prominent nasal bridge, hypertelorism, microphthalmia, micrognathia, prominent low set and slanting ears, and a short neck. However, he did not have severe structural malformation such as CNS, cardiac, genital, limb and gastrointestinal anomalies in spite of the fact that our patient's karyotypes were mosaic pattern without normal one. The difference may be explained by the specific behavior of the ring chromosome and its influence on the clinical characteristics rather than the breakpoints of the chromosome abnormality.

The percentage of a mosaic karyotypes varies depending on the number and type of cells involved[19]. We did not perform a chromosomal analysis on cell types other than the peripheral lymphocyte. In addition, although chromosomal studies of the parents were needed for the assessment of risk in future pregnancies, we could not performed it because they refused further examinations.

한 글 요 약

13번 환염색체의 모자이크 증후군

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김수영 · 오수민 · 김미정 · 송은송
김영옥 · 최영륜 · 우영종 · 황태주

13번 환염색체 증후군은 정신발달의 지체, 성장 장애, 안면부 기형, 중추신경계 기형, 심장기형, 손발의 기형, 골격계 기형 및 항문기형의 특징을 가진다. 많은 수의 13번 환염색체 증후군에 대한 보고가 있었지만 국내에서는 오직 6예의 임상증례 고가 있다. 이들 보고는 모두 순수한 13번 환염색체 증후군을 보고한 것으로 본 저자들은 13번 환염색체 모자이크 현상의 증례를 경험하였다. 산전진찰 상 자궁내 발육지연이 의심되었던 남아에서 안면부기형이 관찰되었으나 이 외에 이학적 검사상 심장 기형, 골격계 및 외부 생식기 기형은 특별히 관찰되지 않았다. 시행한 세포 유전학 검사상 13번 염색체의 ring/monosomy/dicentric 모자이크 현상이 나타났다. 이후에도 근력저하, 성장과 발달지연을 보이고 있다. 저자들은 안면부 기형, 소두증과 대칭성 자궁내 발육지연을 보인 남아에서 13번 환염색체의 모자이크 증후군을 경험하여 기존에 보고된 다른 증례들과 임상 양상을 비교하여 보고하는 바이다.

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