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■ Case report ■

Partial trisomy of chromosome 18q11.2-q12: A case report

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= Abstract =

Edwards syndrome, also called trisomy 18, is one of the most common autosomal anomalies. The survival rate of patients with Edwards syndrome is very low and its characteristic findings include cardiac malformations, mental retardation, growth retardation, specific craniofacial anomalies, clenched hands, rocker-bottom feet, and omphalocele. Compared with the classic Edwards syndrome, the symptom of partial duplication of chromosome 18 is relatively mild with a good prognosis. We report the case of a baby with partial duplication 18q11.2-q12. The characteristic phenotype features of Edwards syndrome were observed in the patient. However, the symptom was milder than the typical Edwards syndrome. At present, we can expect better prognosis for this patient. (Korean J Pediatr 2009;52:1171-1174)

Key Words : Edwards syndrome, Partial trisomy 18, Prognosis

Introduction

Edwards syndrome occurs in approximately 1 of 8,000 live-born infants[1, 2]. It is associated with severe mental retardation and multiple physical malformations including microcephaly, myelomeningocele, omphalocele, cardiac and renal malformations resulting in early mortality[1]. Eighty percent of this syndrome cases have full trisomy, the rest have mosaic or partial trisomy 18 resulting from various abnormalities of chromosome 18 such as duplications, additional isochromosomes of the short arm or long arm and translocations involving other autosomal chromosomes[2]. Compared with classic Edwards syndrome, patients with partial trisomy 18 represent a relatively mild phenotype and show a high survival rate. We present the case of patient with partial trisomy 18 that has a good prognosis

Case Report

He was born at 41 weeks of gestation from a 33-year-old primipara by spontaneous vaginal delivery without forceps assistance or vacuum extraction. His birth weight was 2,750 g and Apgar scores was 8 at 1 minute and 9 at 5 minutes, respectively. After delivery, the child showed the following clinical findings: microcephaly, micrognathia, hairy face, imperforated anus, rocker-bottom feet, cryptorchidism and external genitalia pigmentation. Cardiac investigation revealed patent ductus artriosus and arterial septal defect (Fig. 1).

Cytogenetic evaluation of peripheral blood revealed partial duplication from chromosome 18q11.2 to 18q12 (Fig. 2). The karyotyping of parents' chromosome was also studied and normal karyotypes were ascertained. The colostomy was done on the 4th day, and anoplasty 6th month after. Patent ductus artriosus was completely closed at 4 months and the size of arterial septal defect decreased with time. His height (74.7 cm) and weight (8.9 kg) were maintained the 50th percentile at 8 months and he showed normal growth pattern.

Discussion

Trisomy 18, Edwards syndrome is the second most common autosomal trisomy with an incidence of 1 in 8,000 live births[1, 2]. Most authorities consider trisomy 18 to be a fatal, congenital disorder with mean survival of 1-3 months[1]. About 95% die in utero, of liveborn infants, only

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50% live to 2 months and only 5-10% will survive their first year of life[2, 3]. Congenital heart disease is the major cause of death[1, 4]. While variability in the expression and severity of associated features exist, there are hallmark features present in a majority of trisomy 18 patients. These features include mental and developmental delay, growth deficiency, abnormal craniofacial profile, clenched hands with overlapping digits, internal organ malformations including inguinal or umbilical hernias, and multiple congenital heart defects[4, 5]. Phenotypic variability within an aneuploid syndrome, as well as overlap in clinical features present in different syndromes, is well known characteristics of chromosome aneuploidy. These characteristics compound the difficulty in establishing a succinct correlation between aneuploidy for a specific chromosome region and the manifestation of specific traits[6]. In fact, phenotypic variability has led to disagreement over specificity versus non-specificity in the pathogenesis of aneuploid phenotypes including trisomy 18 and trisomy 21[7].

Although Edwards syndrome is typically associated with duplication of the entire chromosome 18, several individuals with partial trisomy of chromosome 18 have been reported[6-10]. These patients display a range of severity from a relatively mild phenotype with no internal organ malformations to the classic characteristics of Edwards syndrome[11, 12].

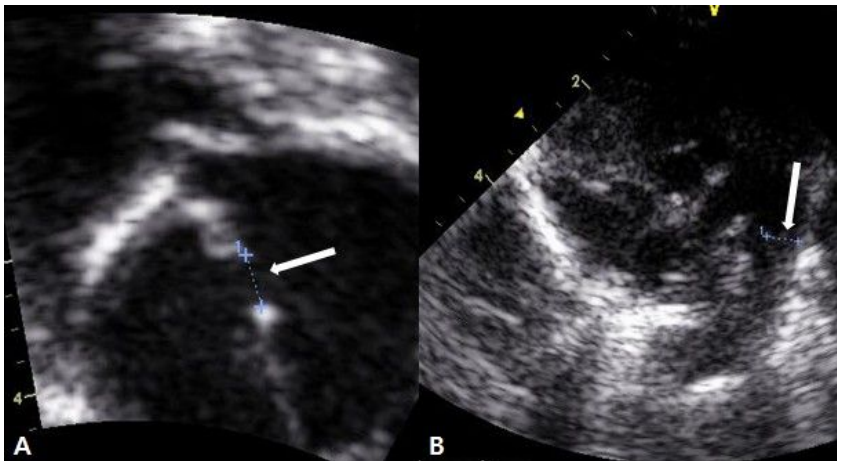

Fig. 1. Transthoracic echocardiography shows arterial septal defect (A) and patent ductus artriosus (B).

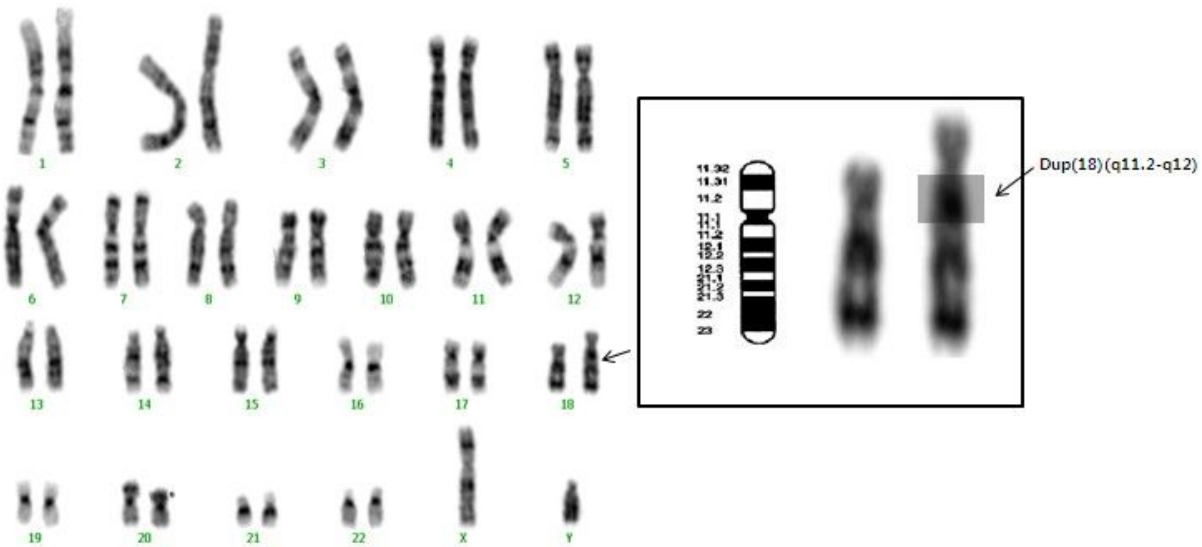

Fig. 2. The karyotype of the patient: 46,XY,dup(18)(q11.2q12).

The triplication of a specific chromosomal region is a reasonable explanation for the appearance of the clinical phenotype for Edwards syndrome. In Down syndrome, extensive molecular analysis has been performed on individuals with partial duplications of chromosome 21. A duplication of only the critical region, 21q22 is sufficient to produce the Down syndrome phenotype[13]. Furthermore, individuals trisomy for other regions of chromosome 21 not including 21q22 do not display the typical clinical picture of Down syndrome[14]. Through the molecular analysis using probes localized to 21q22, the critical region has been narrowed to a level below the limit of cytogenetic detection[15].

But above studies have not been applied to the case of Edwards syndrome. There are several possibilities for why no critical region for Edwards syndrome has been established. Since many of the case reports have been published before high-resolution banding was commonly performed, inaccuracies of the karyotype may have led to misinterpretation of duplicated areas[7, 8, 10, 11]. Alternatively there may be no critical chromosomal region and also the classic phenotype may be due to several noncontiguous chromosomal regions or genes that must be present in three copies to lead to the Edwards syndrome phenotype[16]. The ideal situation for establishing critical region of Edwards syndrome is the analysis of individuals showing pure partial trisomy for chromosome 18. The presence of aneuploidy for other chromosome regions complicates the clinical interpretation[17]. But pure partial duplication of chromosome 18 is a very rare syndrome[16, 18].

In attempts to determine whether and where a critical region for Edwards syndrome exists, different candidate critical regions for Edwards syndrome have been proposed on the basis of the cytogenetic analysis of several patients. One report concluded that the critical region encompasses a region on 18q proximal to 18q12[10], while another report offered an opposing view that the critical region lies in distal 18q, involving band q21[9]. Turleau and de Grouchy[7] proposed that an interaction between 18q11 and 18q22-qter is implicated in the etiology of the trisomy 18 syndrome and further suggested that trisomy of the intermediate segment extending between 18q12 and 18q22 may not associated with the trisomy 18 phenotype. Bogoshian-Sell et al.[17] support the conclusion of Mewar et al.[16] that a region proximal to 18q12 cannot be considered critical to the Edwards syndrome phenotype. Their comparative molecular analysis confirmed that there is no single region on 18q that is sufficient to produce the trisomy 18 phenotype. In conclusion, they identified two regions on 18q that may work in conjunction to produce Edwards syndrome phenotype; a proximal critical (18q12.1-18q21.2) and a distal critical region (18q 22.3-qter). In addition, correlative analysis indicated that duplication of 18q12.3-q21.1 may be associated with the severe mental retardation[17] and also partial region of these parts is duplicated in our patient.

As mentioned above, trisomy 18 has a very high mortality rate and thus there were almost no reported cases of partial trisomy 18. This case was the first reported partial trisomy 18 case in Korea. He had Edwards syndrome symptoms such as microcephaly, micrognathia, imperforated anus, rocker-bottom feet, cryptorchidism, and cardiac diseases. We think that he had a relatively mild phenotype because he had duplication in chromosome 18q12, which is only limited part of the distinctive region for Edwards syndrome, rather than in its entirety. Reconstruction of Imperforated anus was successful with no complication and his cardiac problem resolved itself. After 8 months, we did not detect growth delay. We expect he will have a good prognosis compared with classical Edwards syndrome. But we need to attend his mental development because his duplicated region may be responsible to mental retardation.

한 글 요 약

18q11.2-q12 부분 삼염색체 1예

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에드워드 증후군이라 불리는 삼염색체 18은 실제 생존율이 매우 낮으며 생존한 태아도 복합적 기형과 심한 발육지연으로 생존 태아의 90%는 생후 1년 내에 사망하는 것으로 알려져 있다. 18번 염색체의 전체중복이 주된 원인이며, 부분중복 역시 중복된 부위에 따라 어느 정도 차이는 있으나 에드워드 증후군의 특징적인 임상 양상을 나타낸다. 18번 염색체의 q12.1-q21.2, q22.3-qter부위가 에드워드 증후군의 표현형을 결정하는 부위일 것이라 생각되며 이중 일부만 중복되었을 경우 가벼운 임상 양상 및 좋은 예후를 예측할 수 있다. 본 증례에서 환아는 에드워드 증후군의 표현형을 결정하는 18번 염색체의 q12부위가 포함되어 있는 q11.2-12부위에 부분중복이 관찰되었다. 환아는 전형적인 에드워드 증후군 환자보다 훨씬

가벼운 임상 증상과 높은 생존율이 기대되므로 이와 같이 보고하는 바이다.

References

1) De Grouchy J, Turleau C. Clinical atlas of human chromosomes. 2nd ed. New York: John Wiley & Sons, 1984;292-7.
2) Morallo LM, Rosenblum H, Esterly KL, Johnson WD, Storlazzi JJ, Narvaez AC, et al. Trisomy 18 (Edward syndrome) in Delaware. Del Med J 1983;55:27.
3) Bundy AL, Saltzman DH, Pober B, Fine C, Emerson D, Doubilet PM. Antenatal sonographic findings in trisomy 18. J ultrasound Med 1986;5:361-4.
4) Van Dyke DC, Allen M. Clinical management considerations in long-term survivors with trisomy 18. Pediatrics 1990;85: 753-9.
5) Jones KL. Smith's recognizable patterns of human malformation. 5th ed. Philadelphia: WB Saunders Co, 1997:14-7.
6) Golder N, Wilson G. Karyotype/phenotype controversy: genetics and molecular implications of alternative hypotheses. Am J Med Genet 1990;36:500-5.
7) Turleau C, de Grouchy J. Trisomy 18qter and trisomy mapping of chromosome 18. Clin Genet 1997;12:361-71.
8) Turleau C, Chavin-Colin F, Narbouton R, Asensi D, de Grouchy. Trisomy 18q-: trisomy mapping of chromosome 18 revisited. Clin Genet 1980;18:20-6.
9) Matsuoka R, Matsuyama S, Yamamoto Y, Kuroki Y, MatsuiI. Trisomy 18q: a case report and review of karyotype-phenotype correlations. Hum Genet 1981;57:78-82.
10) Muecke J, Trautmann U, Sandig K-R, Theile H. The crucial band for phenotype of trisomy 18. Hum Genet 1982;60:205.
11) Neu RL, Ortega CC, Barg GA, Pinto W, Gardener LI, Howell WM, et al. Inclusion of satellites in a 18/21 translocation shown by ammoniacal-silver staining (sat-banding) in a case of partial trisomy 18. J Med Genet 1976;13:520-2.
12) Fryns JP, Vinken L, Marien J, Van den Berghe H. Partial trisomy 18q12, due to intrachromosomal duplication, is not associated with typical 18 trisomy phenotype. Hum Genet 1979;46:341-4.
13) Niebuhr E. Down's syndrome: the possibility of a pathogenic segment on chromosome no 21. Humangenetik 1974;21:99-101.
14) Park JP, WursterHill D, Andrews PA, Cooley WC, Graham JMJ. Free proximal trisomy 21 without the Down syndrome. Clin Genet 1987;32:342-8.
15) Korenberg JR, Kawashima H, Pulst SM, Ikeuchi T, Ogasawara N, Yamamoto K, et al. Molecular definition of a region of chromosome 21 that causes features of the Down syndrome phenotype. Am J Hum Genet 1990;47:236-46.
16) Mewar R, Kline AD, Harrison W, Rojas K, Greenberg K, Overhauser J. Clinical and molecular evaluation of four patients with partial duplication of the long arm of chromosome 18. Am J Hum Genet 1993;53:1269-78.
17) Boghosian-Sell L, Mewar R, Harrison W, Shapiro RM, Zackai EH, Carey J, et al. Molecular mapping of the Edwards Syndrome phenotype to two noncontiguous regions on chromosome 18. Am J Hum Genet. 1994;55:476-83.
18) Kleczkowska A, Fryns JP, Buttiens M, De Bisschop F, Emmery L, Van den Berghe H. Trisomy (18q) and tetrasomy (18p) resulting from isochromosome formation. Clin Genet 1986;40:503-8.