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□ 증례 □

A Case of Constitutional Trisomy 8 Mosaicism

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—Abstract—

Constitutional trisomy 8 is a relatively rare aneuploidy; most identified cases are mosaic with a normal cell line. The phenotype is highly variable from apparently normal to severe disability. The proportion of abnormal cells is dramatically different between tissues and the severity of the phenotype is not directly related to the level of mosaicism. Therefore, it is very difficult to provide a definitive prognosis. We report here a case of constitutional trisomy 8 mosaicism with agenesis of the corpus callosum, congenital heart disease and micrognathia. The trisomy 8 cell line was not detected by prenatal cytogenetic study. This is the fourth reported case of constitutional trisomy 8 mosaicism in Korea.

Key Words: Constitutional trisomy 8, Mosaicism, Agenesis of the corpus callosum

INTRODUCTION

Constitutional trisomy 8 is a relatively rare aneuploidy in humans; the incidence has been reported to be about one in 25,000 to 50,000 newborns. It is found with a higher frequency in males than females.[1, 2] Most, perhaps all, cases are mosaic with a normal cell line.[3-5] The phenotype for constitutional trisomy 8 mosaicism (CT8M) is highly variable and has been reported to be apparently normal as well as severely disabled. There seems to be a fairly characteristic phenotype similar to that of the Warkany syndrome.[6] We report here a case of CT8M. Based on our literature review, this is the fourth reported case of CT8M in Korea.[7-9]

CASE REPORT

Our patient was the second child born to a 38-year-old mother and an unrelated

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41-year-old father. Fetal ultrasound was significant for the finding of dilatation of both lateral ventricles. Prenatal cytogenetics and TORCH both were normal. The baby was born at 38.6 weeks gestation by normal spontaneous vaginal delivery. His birth weight was 2.95 kg (25th-50th percentile), his occipito-frontal circumference 35 cm (75th-90th percentile) and his length 50 cm (50th percentile). The Apgar score was 9 at birth. On physical examination, he had asymmetrical micrognathia and a right sided hydrocele. The general condition was good with normal muscle tone and reflexes. An MRI of the brain showed agenesis of the corpus callosum. A 5-6 mm ventricular septal defect (VSD) and a 3 mm atrial septal defect (ASD) were observed on echocardiogram. Two months later, the ASD spontaneously closed. There were no ophthalmic abnormalities on examination. The renal ultrasound was normal. Cytogenetic analysis from a peripheral blood sample was obtained from a phytohemagglutinin-stimulated lymphocyte

Fig. 2. Trisomy 8 mosaicism is demonstrated by fluorescence in situ hybridization with CEP8 probe. Two cells have 3 signals (trisomy 8) and the other two cells have 2 signals (disomy 8).

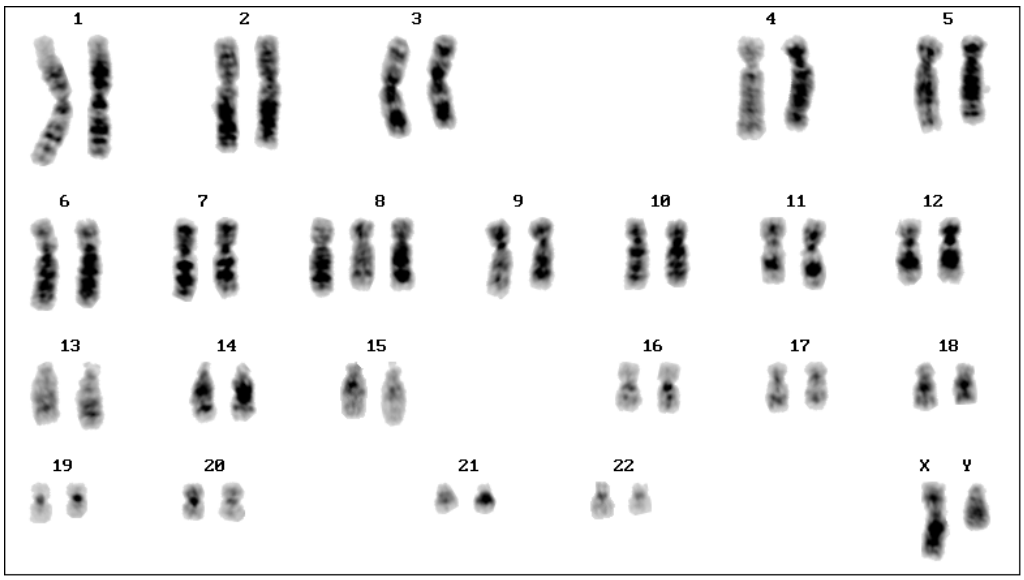

Fig. 1. G-banded karyotype is 47,XY,+8.

culture. The karyotypes were described according to the International System for Human Cytogenetics Nomenclature (ISCN) 1995.10) The karyotype was 47,XY,+8[9]/46,XY[11] (Fig. 1). CT8M was confirmed by fluorescence in situ hybridization (FISH) with chromosome enumeration probe 8 (CEP8) probe (vysis, Downers Grove, IL, USA) (Fig. 2). The disomy 8 : trisomy 8 ratio was 2.3 : 1 by FISH. Parental and sibling karyotype could not be obtained.

DISCUSSION

Trisomy 8 mosaicism can be constitutional or acquired. Constitutional trisomy 8 is a relatively rare aneuploidy, and occurs in less than one in 25,000 live births. The sex ratio is 3:1 male to female. The majority of reported cases of constitutional trisomy 8 are mosaic with a normal cell line. Full trisomy 8 has been reported to be incompatible with life; therefore, survival may be possible only when mosaicism is present.[1-6)]

Patients with trisomy 8 mosaicism, or Warkany syndrome, have variable phenotypic features, such as: deformed skull, prominent forehead, agenesis of corpus callosum, high-arched palate, low-set and/or dysplastic ears, deep palmar and plantar furrows, absent patellae and reduced joint mobility. This variable phenotype also includes mental retardation, which can range from mild to severe.[6, 11-13)] Although the etiology of agenesis of the corpus callosum is assumed to be multifactorial, it is a common feature of CT8M. When it is associated with trisomy 8, it appears to result from duplication of a gene located within 8p21-pter. Most patients are mentally retarded or developmentally delayed, and some have a history of seizures or cerebral palsy.[14, 15)] Cardiovascular malformations, also present in our patient, seem to be less frequently present in reported cases of CT8M where a 50% frequency of congenital heart disease is noted.[16)] The severity of the phenotype associated with CT8M is not directly related to the level of mosaicism. The exact mechanism underlying the severity of the phenotype is still unknown. The absence of a correlation between the level of mosaicism and the phenotype makes it very difficult to provide a definitive prognosis.[17)]

One common finding in patients with CT8M is the dramatic difference in the proportion of abnormal cells in different tissues such as fibroblasts, peripheral blood T or B lymphocytes, bone marrow, amnion and chorion. It has been suggested that the basis of the phenotypic variability may be due to the presence of different proportions of trisomy 8 cells in different body tissues.[11, 17-19)] In addition, the percentage of trisomy cell lines has been noted to be significantly different in interphase and metaphase cells. Trisomy cells are usually more commonly observed in interphase rather than metaphase.

Mechanisms that may be responsible for the significant decrease of trisomy 8 cells in metaphase include varying cellular growth rates, anaphase lag and entry into the G0 phase or apoptosis. According to Hulley,[17] entering the G0 phase may be the most likely mechanism. Passage into the G0 phase would inhibit the progression into mitosis, therefore resulting in a decrease in the number of metaphase cells. Our patient had a normal karyotype in prenatal testing. This might have been due to an extremely low level of mosaicism in amniotic fluid or to a selective growth disadvantage of the trisomy 8 cell line in culture.

The presence of trisomic cells in the embryonic and extra-embryonic tissues confirms the early timing of the mitotic non-disjunction before the embryonic and placental lineages separated. The lower level of trisomy 8 cells in the placental tissues could provide an explanation for the pregnancy progressing to full term with normal birth weight, despite the severity of the patient's phenotype.[17]

Acquired trisomy 8 is one of the most common chromosomal abnormalities associated with myeloid malignancy.[20] Thirteen cases of hematologic malignancies in patients with CT8M have been reported. Interestingly most cases, except for one case, were myeloid malignancy.[21] In a case of chronic myelomonocytic leukemia, which developed in a patient with constitutional partial trisomy 8 mosaicism, the partial trisomy 8 cell line was seen in all of the examined bone marrow cells. It had been suggested that CT8M predisposed this patient development of myeloid malignany.[12] Therefore, we plan to monitor our patient for the risk of developing a neoplasm.

요 약

체질성 8세염색체는 비교적 드문 염색체 이상으로 신생아 25,000-50,000명당 한 명 정도의 출생빈도를 보이며 여아보다 남아에서 발생빈도가 높다. 순수한 8세염색체는 생존이 어려운 것으로 보이며 보고된 대부분의 증례는 섞임증이다. 저자들은 뇌량 무발생, 선천성 심장질환과 소악증을 가진 신생아에서 말초혈액 T 림프구 핵형분석 및 형광동소교잡법을 통해 체질성 선천성 8세염색체 섞임증을 진단하였다. 체질성 8세염색체 섞임증의 표현형은 거의 정상에 가까운 형태에서 심한 신체적 혹은 지능장애까지 매우 다양하지만 그 표현형의 정도가 전체 핵형에서 8세염색체 핵형이 차지하는 비율, 즉 섞임증의 정도와 비례하지는 않는다. 또한 조직마다 섞임증의 정도가 매우 다양하여 그 예후를 예측하기는 매우 어렵다. 8세염색체 세포에서 골수성 혈액질환의 발생빈도가 높은 것으로 알려져 있으므로 향후 주의깊은 추적관찰이 필요하다.

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