Holoprosencephaly: A Rare Finding in Mosaic Trisomy 9 Syndrome

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ABSTRACT

Mosaic trisomy 9 syndrome is a rare chromosomal abnormality and is well defined with dysmorphologic features such as upslanting and short palpebral fissures; deeply set eyes; micrognathia; and cardiovascular, genital, and brain abnormalities. Holoprosencephaly, a developmental brain abnormality, is a rarely seen in patients with mosaic trisomy 9 syndrome. Here we present a case of a patient with mosaic trisomy 9 syndrome with alobar type holoprosencephaly who died in the first hour of the natal period. As per the literature, this is the third case of mosaic trisomy 9 with holoprosencephaly to be reported. Therefore, we believe that holoprosencephaly might take part among the classic dysmorphic features of mosaic trisomy 9 syndrome.

Keywords: Holoprosencephaly, mosaic trisomy 9, PTCH1

INTRODUCTION

Holoprosencephaly (HPE), one of the most common developmental anomalies of the brain, is a clinical presentation resulting from the failure of the prosencephalon to develop into two hemispheres in the early stages of embryogenesis (1). Even though HPE, which displays genetic heterogeneity, can occur alongside numerical and structural chromosomal abnormalities, it is also associated with monogenic and oligogenic syndromes as well as environmental factors. While chromosomal abnormalities are identified in 24%-45% of HPE cases, trisomy 13 is most frequently reported (2, 3). The case of holoprosencephaly presented here is accompanied by mosaic trisomy 9 syndrome, and based on our research, this is the third such reported case in the literature (4, 5).

CASE REPORT

Fetal ultrasound and echocardiography performed on the fetus of a 36-year-old woman during her first pregnancy within the 21st week of gestation revealed intrauterine growth retardation (IUGR), absent nasal bone, bilateral microphthalmia, holoprosencephaly, diaphragmatic hernia, atrioventricular septal defect, tricuspid atresia, and pulmonary hypoplasia. The family, who were recommended amniocentesis, refused the invasive procedure, and the baby was born through spontaneous vaginal delivery in the 39th week of pregnancy, with an Apgar score of 3/6. The infant developed cardiopulmonary arrest and was unresponsive to resuscitation, resulting in death.

The deceased female infant was referred to our medical genetics department for genetic examination. A post-mortem dysmorphological examination of the infant resulted in the discovery of brachycephaly, narrow forehead, hypotelorism, deeply set eyes, microphthalmia, flattened nasal bridge with one nostril, posteriorly rotated ears, camptodactyly, and bilateral single palmar crease (Figures 1 and 2). Post-mortem brain tomography of the infant revealed alobar holoprosencephaly (Figure 3), and the cytogenetic analysis of the fibroblast cell culture from two separate flasks of skin biopsy from the antecubital region of the infant revealed mosaic trisomy 9 syndrome (mos 47,XX,+9[6]/46,XX[54]).

In this present case, the study of possible mutations, mainly in genes such as sonic hedgehog (SHH) and PTCH1, related with the etiology of HPE, could not be performed because the limited amount of post-mortem skin material was used up in the long-term tissue culture to obtain the metaphase plaques.

DISCUSSION

Mosaic trisomy 9 syndrome is a rare chromosomal anomaly wherein the affected cases usually exhibit IUGR, micrognathia, low-set ears, rocker-bottom feet, and congenital heart anomalies. In certain rarer cases, various anomalies of the central nervous system, including hydrocephaly, lissencephaly, and agenesis of the corpus callosum as well as microcephaly, microphthalmia, cleft lip and palate, diaphragmatic hernia, simian crease, and
genitourinary anomalies, can also be seen (6). Holoprosencephaly is a heterogeneous clinical situation linked to various genetic components where chromosomal aberrations also play a role. Non-syndromic holoprosencephaly can be related with heterozygous mutation of the SHH, ZIC2, SIX3, and TIGF1 genes; however, in rare cases, a possible link to the patched1 (PTCH1) gene localized to the ninth chromosome and that suppresses the SHH pathway has also been reported (7). SHH, a morphogen that plays a role in the reproduction, position, and organization of cells within developing tissue during the embryonic stage, is linked to Type 3 HPE (MIM: 142945), and the PTCH1 gene that encodes the receptors for SHH is linked to Type 7 HPE (MIM: 610828) (8, 9). In addition to suppressing the SHH pathway, a further relation is also suggested between HPE and a mutation or gene duplication resulting in an increase in the functions of the PTCH1 gene (10).

In the present case, the study of possible mutations, particularly in genes such as SHH and PTCH1 related with the etiology of HPE, could not be performed, as the limited amount of post-mortem skin material was used up in the long-term tissue culture to obtain the metaphase plaques.

Two other cases with similar clinical findings to ours (lUGR, flattened nasal bridge, low-set ears, ventricular septal defect), where HPE and mosaic trisomy 9 syndrome are found together, exist in the literature. In contrast to our case, HPE is of the lobar type in these cases (4, 5). In addition, no HPE was discovered in the brain tomography of the Kaminker et al. (11) case diagnosed with mosaic trisomy 9 syndrome. Nevertheless, taking into account the imaging technology available at the time, it is possible that either HPE was not discovered or the case may have been a microform of HPE. Moreover, holoprosencephaly detected in our case may have developed as a result of a dose increase in the PTCH1 gene located on the ninth chromosome. Structural brain abnormalities such as lissencephaly, hydrocephaly, and corpus callosum agenesis have been reported in a comprehensive study of mosaic trisomy 9 syndrome cases. However, no holoprosencephaly anomaly was detected in any of the 25 patients included in the article (12).

CONCLUSION

The fact that all three independent mosaic trisomy 9 syndrome cases were accompanied by HPE supports the notion that HPE may be a symptom of this aneuploidy as well as the suggestion by other researchers that gain-of-function mutations of the PTCH1 gene may also cause HPE. However, further research is needed to explain why this symptom is not present in all trisomy 9 cases.

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REFERENCES

1. Lacbawan F, Solomon BD, Roessler E, El-Jaick K, Domené S, Vélez JL, et al. Clinical spectrum of SIX3-associated mutations in holoprosencephaly: correlation between genotype, phenotype and function. J Med Genet 2009; 46(6): 389-98. [CrossRef]

2. Croen LA, Shaw GM, Lammer EJ. Holoprosencephaly: epidemiologic and clinical characteristics of a California population. Am J Med Genet 1996; 64(3): 465-72. [CrossRef]

3. Olsen CL, Hughes JP, Youngblood LG, Sharpe-Stimac M. Epidemiology of holoprosencephaly and phenotypic characteristics of affected children: New York State, 1984-1989. Am J Med Genet 1997; 73(2): 217-26. [CrossRef]

4. Gerard-Blanluet M, Danan C, Sinico M, Lelong F, Dassieu G, et al. Mosaic trisomy 9 and lobar holoprosencephaly. Am J Med Genet 2002;111(3): 295-300. [CrossRef]

5. Yang Z. Mosaic Trisomy 9 in a Male Fetus with Severe Facial Abnormality and Genital Hypoplasia. Int J Hum Genet 2013; 13(2): 75-8. [CrossRef]

6. Jones KL, Jones MC, Del Campo M. Trisomy 9 Mosaic Syndrome. Smith’s Recognizable Patterns of Human Malformation. 7th edition. USA: Elsevier Health Sciences; 2013.p.28-9.

7. Mouden C, Dubourg C, Carré W, Rose S, Quelin C, Aldol L, et al. Complex mode of inheritance in holoprosencephaly revealed by whole exome sequencing. Clin Genet 2016; 89(6): 659-68. [CrossRef]

8. Roesslerl E, Belloniz E, Gaudenzl K, Iay P, Berta P, Schererz SW, et al. Mutations in the human Sonic Hedgehog gene cause holoprosencephaly. Nat Genet 1996; 14(3): 357-60. [CrossRef]

9. Towers M, Wolpert L, Tickle C. Gradients of signalling in the developing limb. Curr Opin Cell Biol 2012; 24(2): 181-7. [CrossRef]

10. Derwińska K, Smyk M, Cooper ML, Bader P, Cheung SW, Stankiewicz JF. Mosaic trisomy 9 syndrome with unusual phenotype. Am J Med Genet 1985; 22(2): 237-41. [CrossRef]

11. Bruns DA, Campbell E. Twenty-five additional cases of trisomy 9 mosaic: Birth information, medical conditions, and developmental status. Am J Med Genet A 2015; 167A(5): 997-1007. [CrossRef]