



## Holoprosencephaly: A Rare Finding in Mosaic Trisomy 9 Syndrome

CASE REPORT

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ABSTRACT

Mosaic trisomy 9 syndrome is a rare chromosomal abnormality and is well defined with dysmorphic 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 39<sup>th</sup> 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 dysmorphic 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

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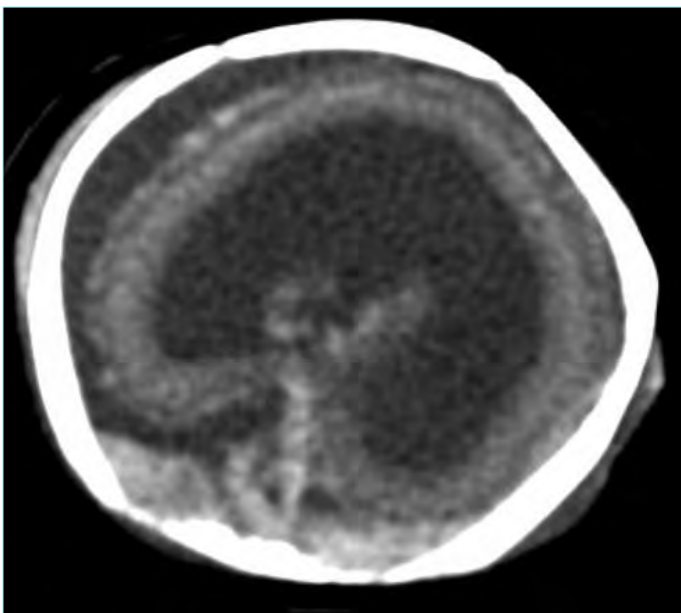
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**Figure 1.** Hypotelorism, flat nasal bridge, and microphthalmia



**Figure 2.** Single nostril



**Figure 3.** Alobar holoprosencephaly in post-mortem cranial CT

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. Nonsyndromic 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 (IUGR, 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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