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# HOLOPROSENCEPHALY ANOMALY WITH NASAL AND PREMAXILLAR AGENESIS*
## (Possibly Autosomal Recessive Type)

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**SUMMARY: Aydoğdu Durmuş S, Yakut A, Öner Ü, Akşit MA, Tel N. (Departments of Pediatrics and Pathology, Anadolu University Faculty of Medicine, Eskişehir, Turkey). Holoprosencephaly anomaly with nasal and premaxillar agenesis. Turk J Pediatr 1994; 36: 157-162.**

**A one-day-old male infant with cleft lip and palate, microcephaly, hypotelorism, microphthalmia and absence of the nose is presented. The intermaxillar segment and nasal bone structure were not seen on radiological examination of the skull. Chromosome examination showed a 46, XY karyotype. On postmortem examination, the cerebrum was seen to be a single lobe. Olfactory nerves, corpus callosum and nasal formation, besides the septum were absent. The first and second ventricles were formed as a single ventricle. These findings were compatible with alobar holoprosencephaly.** *Key words: holoprosencephaly, nasal and premaxillar agenesis.*

Holoprosencephaly is a malformation complex in which impaired midline cleavage of the embrionic forebrain is the basic feature[1]. The term "arhinencephaly" was used in 1882 by Kundrat because of the hypoplasia or absence of the olfactory bulbs and tracts[2] DeMyer and Zeman[3] used the term "holoprosencephaly" and classified this condition according to the degree of severity as alobar, semilobar and lobar formation.

The true incidence of holoprosencephaly is unknown. In the study by Cohen[4] the prevalence was given as 0.56/10,000-0.63/10,000 in live births.

In this article, a male infant with alobar holoprosencephaly associated with nasal agenesis, which is seen very rarely, and premaxillar agenesis, who exhibited normal karyotype is presented. Related literature is reviewed.

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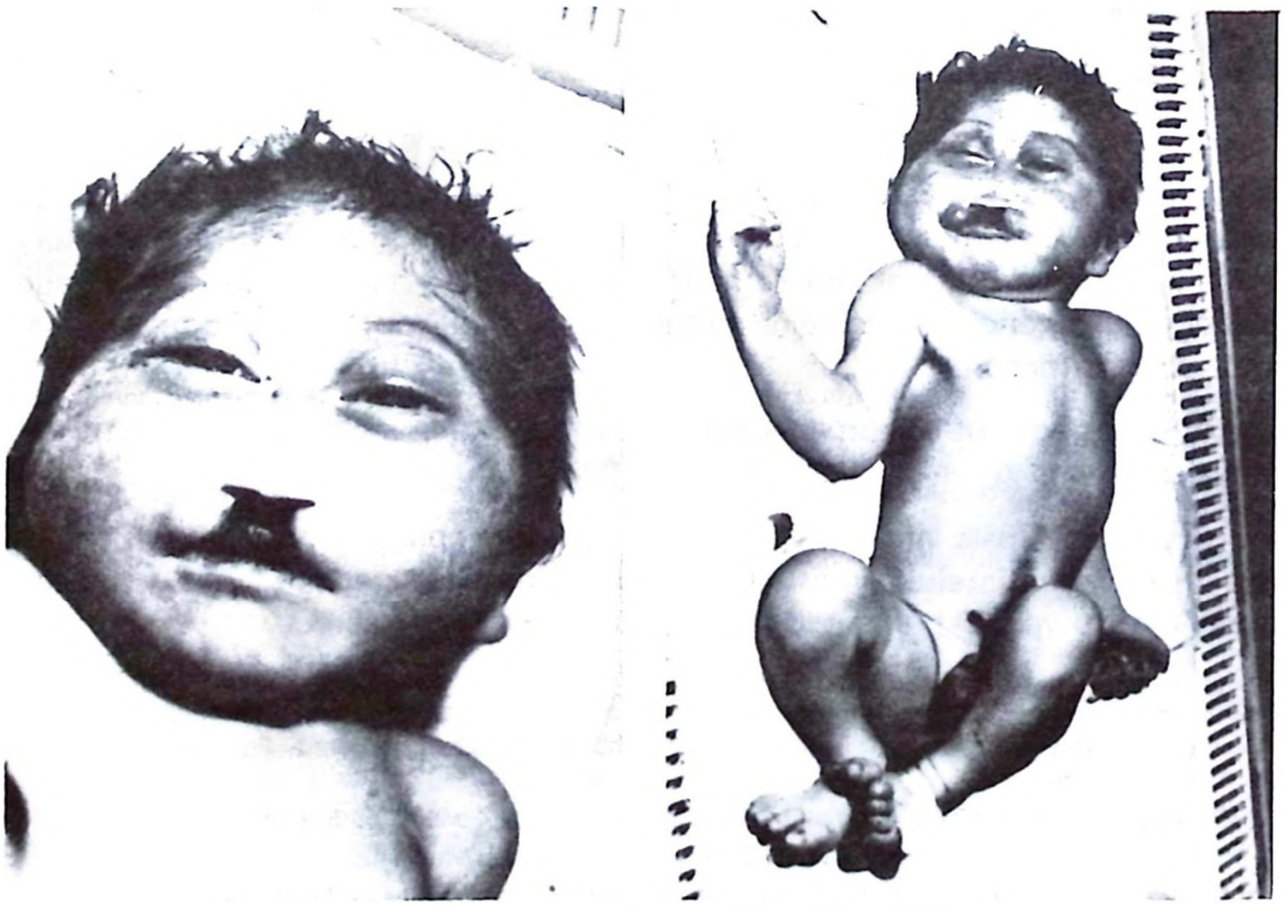
## Case Report

A one-day-old male infant was admitted to the hospital because of cleft lip and palate and hypotelorism. He was born at 38 weeks gestation with an uncomplicated delivery as the product of the first pregnancy of a 22-year-old mother. His parents were first-degree relatives. There was no history of congenital anomaly in the family. The parents had a normal female baby after this child.

Physical examination revealed that his weight was 2800 g. length was 49 cm, and head circumference was 31 cm. He had a narrow forehead, hypotelorism, bilateral proptosis and microphthalmia, a short neck, low-set ears with folded auricula on the right side, and complete cleft lip and palate. There was no outer nose formation, but the nasal septum could be seen when looked through the mouth (Figs. 1 and 2). The patient had tachypnea, and crackling rales were heard on auscultation. The Moro reflex was diminished bilaterally.

Laboratory examination revealed that complete blood count, blood glucose, serum electrolytes and calcium were normal. On urinalysis, (+ +) proteinuria and 3-4 leucocytes and granular cylinders were displayed. Proteus (100,000/$mm^3$)

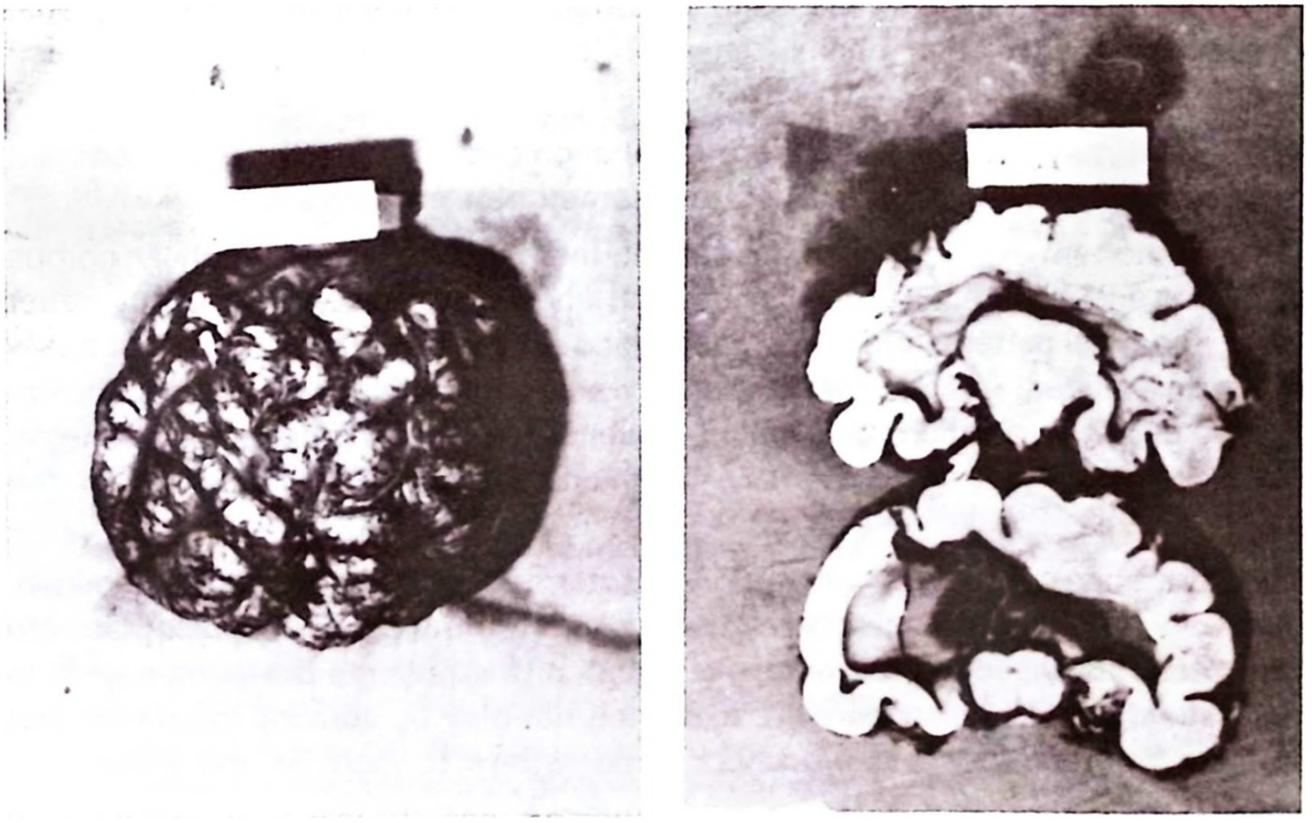


Figs. 1, 2: Face and general appearance of the patient.

was isolated in the urine culture. Craniography showed an absence of the intermaxillar segment and nasal bone structure. The skeletal survey was normal. A chest X-ray demonstrated bilateral bronchopneumonic infiltration. Intravenous pyelography and electrocardiogram were normal. Electroencephalogram showed diffuse irregular activity. Chromosomal examination demonstrated 46, XY karyotype.

During the patient's hospital stay, he was fed by nasogastric tube. Penicillin G. and gentamicin were given for respiratory and urinary tract infections. The patient gradually exhibited difficulty breathing, so nasogastric feeding was stopped. He also had generalized convulsions. The infant's condition deteriorated, and despite supportive treatment he died on the $10^{th}$ day of hospitalization.

The post-mortem examination revealed severe central nervous system malformations. The cerebrum consisted of a single lobe, with a decreased gyral pattern. Frontal lobes were atrophic. There were no olfactory nerves. There was corpus callosum agenesis. No distinction in grey-white substance was observed. The ventricles were not formed properly; the lateral and third ventricles were formed as a single ventricle. The lower portion of the third ventricle was present, but the upper part consisted only of meningeal membranes which formed a sac. The fourth ventricle was absent (Figs. 3 and 4). Besides cerebral malformations the



Figs. 3, 4: Brain as a single lobe and ventricular abnormalities.

right lung consisted of two lobes. In addition, hemorrhagic bronchopneumonia and a slight thymic involution were observed.

## Discussion

Holoprosencephaly has been defined as a medial facio- cerebral developmental abnormality. Cerebral malformations may vary according to the severity of the defect. The term alobar holoprosencephaly or holotelencephaly may be more appropriate in the most common of severe cases, in which the telencephalon remains a single sphered structure but the diencephalon is somewhat less affected[5].

In this anomaly, the olfactory bulbs and tracts are nearly always absent. The term semilobar holoprosencephaly is used to describe a brain with rudimentary hemispheric lobes, an incomplete interhemispheric fissure, and arhinencephaly. The brain with lobar holoprosencephaly has well-formed hemispheric lobes, a distinct interhemispheric fissure, and the third ventricle is continuous with the lateral ventricles[2,3,6,7].

Holoprosencephaly has rarely been associated with several other central nervous system anomalies such as anencephaly, encephalocele, spina bifida and agenesis of cranial nerves[2,8]. Anomalies of other organs are present in 50-60% of patients with holoprosencephaly. The most common anomalies are congenital heart disease, lung anomalies, diaphragmatic defects, omphalocele, hepatic malformation and double vaginae. Endocrine disturbances such as diabetes insipidus, hypoplastic thyroid, and nonexistance of the pituitary gland have also been seen[2,7,8].

Although it may be true that severe facial anomalies can predict a concomitant brain anomaly, facial abnormalities are sometimes mild or absent[2,6,7,9,10].

On post-mortem examination of our patient, tele ventricle, arhinencephaly, corpus callosum agenesis, and atrophy of frontal lobes were observed. On the other hand, the gyral patterns were decreased, and gray-white matter could not easily be differentiated. All of the findings were compatible with alobar holoprosencephaly. In addition, our patient exhibited nasal and premaxillar agenesis. Nasal agenesis is a rare anomaly, with only a few cases reported in the literature[11,12].

Clinically, apneic episodes, convulsions, motor and mental retardation, anosmia, spasticity, hemispheric asynchrony and spikes in the electroencephalogram are most commonly seen in this anomaly[2]. Most of the patients die in infancy[2,6]. In our patient, apneic episodes were explained not only by cerebral anomalies but also by lung anomaly and bronchopneumonia due to cleft lip and palate.

Holoprosencephaly is a heterogenous condition, and the cause is unknown in most cases[2,6,7]. Holoprosencephalic malformations have been produced ex-

perimentally with vitamin D, vinblastine, alcohol and Veratrum Californicum[1,2,7]. Barr et al[13] reported that holoprosencephaly is increased in children of diabetic mothers.

Although holoprosencephaly is usually sporadic and familial autosomal dominant, autosomal recessive and X-linked transmission have also been reported[2,3,6,7,14-17]. On the other hand, numerous chromosomal abnormalities have been described in holoprosencephaly, especially, together with extracranial anomalies such as trisomy D, trisomy 18, Down's syndrome, 18 $p^-$ syndrome, and 13 q syndrome[2,3,6,7,18,19]. Our case had extracranial anomalies and a normal karyogram. Holoprosencephaly has also been associated with other syndromes, such as DiGeorge syndrome, Meckel syndrome, and Kalman's syndrome[27].

Possible autosomal recessive-type holoprosencephaly was detected in our patient. For this reason, genetic counselling is important because of the 25% chance of anomaly in every pregnancy. Prenatal diagnosis can be done by ultrasonography. In Turkey, Balcı et al[20-22] reported cases with autosomal recessive cyclopia/holoprosencephaly anomaly who were diagnosed by ultrasonography at 18 weeks gestation.

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