INTRODUCTION
The combination of holoprosencephaly, cleft lip/palate, and ectodactyly has rarely been reported in the literature.\(^1,2\) Hypernatremia and diabetes insipitus are seldom complication of holoprosencephaly in these patients.\(^3-5\) We report a female patient with a constellation of malformations, including cleft lip/palate, holoprosencephaly, ectrodactyly, and recurrent hypernatremia.

CASE REPORT
A 7-month-old female infant was hospitalized because of hypernatremic dehydration and pneumonia. She was born at 40 weeks of gestation with a birth weight of 3300 g following an uneventful pregnancy. No significant data were mentioned in the family history. On physical examination, her weight, length, and head circumference were all below the third percentile for age. Her physical features included microcephaly, cleft lip and palate, flat nose, ectrodactyly, and psychomotor delay (Figure 1). She showed signs of severe dehydration with an excessively dry tonque and buccal mucosa. She had dyspnea and tachypnea. The laboratory examination revealed the following: hemoglobin 9.6 g/dl (12-14 g/dl), white blood cell 16.900/mm\(^3\) (4000-10,000/mm\(^3\)), and platelet count 436.000/mm\(^3\) (150- 400 x 10\(^3\)).

Erythrocyte sedimentation rate and C-reactive protein were elevated. Biochemistry studies yielded blood urea nitrogen (BUN) 57 mg/dl (10-40 mg/dl), Na 164 mEq/L (135-145 mEq/L), and creatinine 0.12 (0.4-1). Other biochemical parameters were normal. Her chest X-ray revealed bilateral pneumonia infiltration. Her urine sediment was normal. She was administered 20 cc/kg 0.9% saline in the first hour and then 0.2% saline with dextrose was applied within 48 hours as the replacement fluid to reduce brain injury. After the fluid replacement, BUN returned to the normal level. Ceftazidim and aminoglicoside were started for a lower respiratory tract infection. Although we applied appropriate fluid treatment, hypernatremia persisted. We evaluated for persistent hypernatremia. Serum osmolality (332 mosm/l) was elevated while urine osmolality (162 mosm/l) was decreased. Her clinical state deteriorated. Klebsiella pneumoniae was isolated in the hemoculture. The antibiotherapy was changed to imipenem (40 mg/kg) according to the sensitivity pattern of the hemoculture.

Cerebral magnetic resonance imaging showed the Dandy-Walker variant and lobar holoprosencephaly (Figure 2). No conspicuous changes were detected in anterior pituitary function tests. The antidiuretic hormone level (ADH) was low. The water deprivation test was consistent with diabetes insipitus.

Karyotype analysis revealed 46 XX. We scheduled her for treatment with ADH. Despite appropriate antibiotherapy and fluid replacement, she died due to sepsis.
The main signs in our patient were holoprosencephaly, cleft lip and palate, ectrodactyly, hypernatremia, and psychomotor retardation. In the differential diagnosis, we suspected HHES (holoprosencephaly, hypertelorism, ectrodactyly) syndrome. This diagnosis was disregarded since she did not have hyper- or hypotelorism.

Holoprosencephaly is described as a defective cleavage of the forebrain to symmetric cerebral hemispheres. It is classified into three groups depending on the severity of the pathology: alobar, lobar, and semilobar. It includes a spectrum of conditions that have in common the associated anomalies of median cleft lip or palate, nasal malformation, and brain malformations. Complications of holoprosencephaly are diverse and may involve diabetes insipitus, neurogenic hypernatremia, and hypopituitarism. Hypernatremia or diabetes insipitus occurring in holoprosencephaly may be explained by functional or structural pathologies of the hypothalamohypophyseal axis.

Case notes of patients with holoprosencephaly have shown that in clinical trials of adipsia or hypodipsia associated with hypernatremia ADH secretion is decreased. Plasma osmolality and hypernatremia can be corrected by the administration of ADH. When we reviewed the literature, we found just a few patients with holoprosencephaly, cleft lip and palate, and hypernatremia. In our patient, the serum ADH level was decreased, serum osmolality was increased, and urine osmolality was decreased. These results were consistent with diabetes insipitus. The water deprivation test indicated diabetes insipidus. As shown by its low serum level in our patient, defective synthesis or release of ADH will disrupt renal concentrating capacity and lead to hypernatremia. Holoprosencephaly contributes to this clinical aspect by causing a defect in the thirst mechanism. Therefore, she could not maintain her needs and recurrent hypernatremic episodes occurred.

In hypernatremic dehydration, intracellular water loss is prominent. Therefore, clinical findings that are not compatible with the level of dehydration may occur. Hypernatremia must be corrected slowly to reduce the effect on the central nervous system. In our patient, hypernatremia was corrected in 48 hours as recommended in the literature.

Forty-five percent of live births with holoprosencephaly have been shown to be associated with chromosomal abnormalities but this report does not include milder cases. It may be associated with trisomy 13, trisomy 18, and several multiple malformation syndromes like Pallister-Hall syndrome, Rubinstein Taybi syndrome, and Smith Lemli Opitz syndrome.

DISCUSSION

The main signs in our patient were holoprosencephaly, cleft lip and palate, ectrodactyly, hypernatremia, and psychomotor retardation. In the differential diagnosis, we suspected HHES (holoprosencephaly, hypertelorism, ectrodactyly) syndrome. This diagnosis was disregarded since she did not have hyper- or hypotelorism.

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syndrome. The exact inheritance pattern is not still clear. Eight genes have been found to be associated with holoprosencephaly so far: SHH (7q36), ZIC 2 (13q32), SIX3 (2p21), and TGIF (18p11.3). Although we were unable to perform mutation analysis in our patient, we suggest to perform it in patients with holoprosencephaly to inform the families for the sake of their subsequent children.

We conclude from this case that magnetic resonance imaging of the brain should be performed in patients with midline facial defects and recurrent hypernatremia attacks because of the large possibility of underlying central nervous system malformation. Diabetes insipitus should also be searched for as a complication.

Treating clinicians must always be aware of the complex nature of these patients and their potential for early demise and should inform parents about it.

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REFERENCES