

EARLY-ONSET CENTRAL DIABETES INSIPIDUS IN A NEWBORN WITH HOLOPROSENCEPHALY

HOLOPROZENSEFALİ TANILI BİR YENİDOĞANDA ERKEN BAŞLANGIÇLI SANTRAL DİABETES İNSİPIDUS

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ABSTRACT

Holoprosencephaly is a complex brain malformation caused by the inability of the prosencephalon to divide to form the cerebral hemispheres. Central diabetes insipidus (CDI), as a result of a defect in vasopressin release, may be seen due to the abnormal hypothalamic infundibular region. CDI developing secondary to holoprosencephaly in the early neonatal period has rarely been reported in the literature. A case of early-onset CDI with holoprosencephaly and 13q deletion is presented.

Keywords: Holoprosencephaly, central diabetes insipidus, newborn, desmopressin

ÖZET

Holoprozensefali, prozensefalonun serebral hemisferleri oluşturmak için bölünmesi sırasındaki yetersizlikten kaynaklanan kompleks bir beyin malformasyonudur. Anormal hipotalamik infundibular bölge nedeniyle vazopressin salınımındaki kusura bağlı santral diabetes insipidus (SDİ) görülebilmektedir. Erken neonatal dönemde holoprozensefaliye ikincil gelişen SDİ vakası enderdir. Holoprozensefali ve 13q delesyonu olan erken başlangıçlı bir SDİ vakası sunulmuştur.

Anahtar Kelimeler: Holoprozensefali, santral diabetes insipidus, yenidoğan,

INTRODUCTION

Holoprosencephaly (HPE) is a complex brain malformation caused by the failure of the prosencephalon to divide between the 35th and 42nd days of embryonic life. Depending on the degree of septation deficiency, it can occur in three forms as lobar, semilobar and lobar. The incidence of lobar HPE has been reported to be 0.6-1.9 per 10,000 live births. Holoprosencephaly can either be isolated or accompany various syndromes. The prognosis depends on the severity of the brain and facial deformities along with the presence of related anomalies. Lobar HPE carries the worst prognosis among other prosencephalon division anomalies. Central diabetes insipidus (CDI) may be an accompanying feature due to a defect in vasopressin release as a result of abnormalities in the hypothalamic infundibular region (1, 2).

CASE PRESENTATION

A baby boy with a birth weight of 3,000 grams (AGA) was born to a 34-year-old G₆P₄A₂ mother at 39^{3/7} weeks of gestation. Antenatal ultrasonography (USG) showed that the fetus had HPE and corpus callosum agenesis. After birth the baby was admitted to the neonatal intensive care unit for further investigation and follow-up. The history of the mother revealed two previous pregnancies, one resulting in miscarriage at the 8th week and the other live birth with HPE who died at the age of 5.5 years. No genetic analysis had been performed for either the child who died with holoprosencephaly or the two miscarriages. The parents were first degree cousins. Microcephaly, slanted palpebral fissures, hypotelorism, clinodactyly in the fifth finger of the left hand and mild hypertonicity were detected on physical examination (Figure 1).

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Figure 1: External appearance of the patient

Cranial magnetic resonance imaging showed semilobar HPE with fusion in the thalami, agenesis of corpus callosum and interhemispheric fissure, fusion of lateral ventricles at the corpuscular level and dilatation in the fourth ventricle and cisterns (Figure 2).

In the first three days of life, the baby fed well and there was no pathological weight loss. However, on the 4th postnatal day, polyuria developed (urine output: 5.9 cc/kg/hour). Daily weight loss was high (5.4%/day). Serum biochemistry results were as follows: urea 40.8 mg/dL, creatinine 1.05 mg/dL, BUN 19.7 mg/dL, sodium 149 mEq/L and other electrolytes were normal. Blood gases revealed pH 7.31, pCO₂ 42 mmHg, HCO₃ 20.4 mEq/L, base deficit -2.1 mEq/L, lactate 1.3 mEq/L, and glucose 87 mg/dL. Sepsis markers were negative. Urinary sodium level was 14 mEq/L, urine density was 1,002 while serum osmolarity was 325 mOsm/L. Blood cortisol level

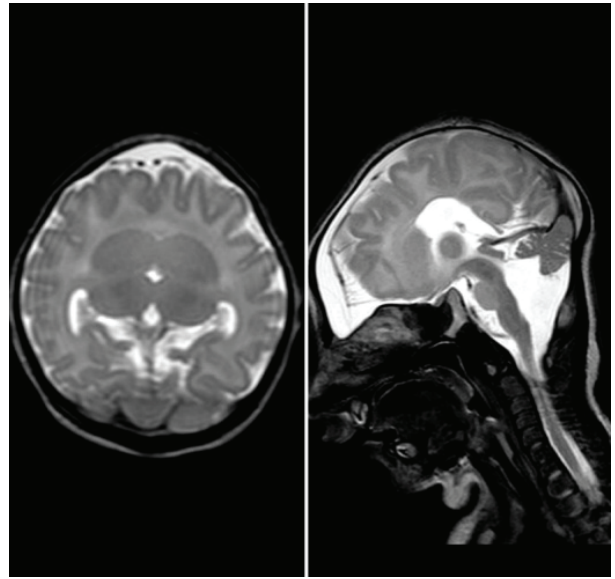


Figure 2: Cranial magnetic resonance imaging sections (holoprosencephaly and corpus callosum agenesis)

(6.26 mcg/dL), renin activity (4.02 ng/mL/hour), aldosterone level (80.7 ng/dL) and thyroid function tests (thyroid stimulating hormone (TSH) 5.21 pmol/L, free thyroxine (T₄) 25.1 mIU/L) were normal. Although enteral feeding and parenteral fluid support was gradually increased to a total of 250 cc/kg/day, polyuria continued and serum sodium levels increased (156 mEq/L) on the postnatal 5th day. Oral desmopressin 1.2 µg/day was started and the dose was increased to 2.4 µg/day according to the clinical findings and laboratory results of the patient. On the 3rd day of the treatment, blood sodium levels and urine output returned to normal values (Table 1). Parenteral fluid support was gradually decreased while oral intake was increased. On the postnatal 9th day, parenteral fluids were discontinued completely. The genetic test results showed a deletion in the long arm on the chromosome 13. On the postnatal 11th day, the baby started to gain weight and his laboratory values and urine output were normal. The patient, who did not need parenteral fluid support and was fed with breast milk, was discharged with oral desmopressin treatment (2.4 µg/day)

DISCUSSION

Holoprosencephaly (HPE) is the most common malformation of the prosencephalon, which cannot be separated into two hemispheres and ventricles. It is a midline growth and separation defect characterized by severe malformations of the face and brain, often resulting in intrauterine death. Approximately 25-50% of individuals with HPE have a chromosomal abnormality. Chromosomal abnormalities are nonspecific and either numeric or structural, and can involve any chromosome (3). The region on chromosome 13q contains the *ZIC2*

Table 1: Follow-up during hospitalization

Days of life	1	2	3	4	5	6	7	8	9	10	11
Total fluid (mL/kg/day)	Breastfeeding	Breastfeeding	Breastfeeding	150 (Breastfeeding and parenteral fluid)	200 (Breastfeeding and parenteral fluid)	250 (Breastfeeding and parenteral fluid)	200 (Breastfeeding and parenteral fluid)	180 (Breastfeeding and parenteral fluid)	Breastfeeding	Breastfeeding	Breastfeeding
Daily weight difference (%)	-1.2	-2.5	-3.1	-5.4	-2.1	-1.5	+3.6	+3.4	+2.9	+1.4	+0.9
Serum sodium (mEq/L)	-	-	146	149	156	151	144	142	140	138	139
Serum osmolarity (mOsm/L)	-	-	-	325	332	304	297	289	278	280	-
Diuresis (cc/kg/hour)	-	-	-	5.9	5.4	4.1	2.3	2.0	2.5	2.1	2.2
Urine osmolarity (mOsm/L)	-	-	-	79	75	108	197	264	262	256	-
Urine density	-	-	-	1002	1002	1003	1009	1011	1011	1010	1011
Spot urine sodium (mEq/L)	-	-	-	14	10	19	17	15	18	16	-
Oral desmopressin dose (µg/day)	-	-	-	-	1.2	2.4	2.4	2.4	2.4	2.4	2.4

gene. The *ZIC2* transcription factor is one of the most commonly mutated genes in HPE probands (4). The genetic test results of our case showed a deletion in the long arm on the chromosome 13. However as genetic analysis had not been performed for either the child who died with holoprosencephaly or the two miscarriages, nor the parents, we could not comment on the inheritance model of HPE seen in this index case.

Central diabetes insipidus (CDI) is a disease characterized by hypernatremia, hypostenuria and polyuria that develops due to a deficiency of antidiuretic hormone (ADH) secretion from the posterior pituitary. CDI in the neonatal period generally develops as a complication of intrauterine and perinatal diseases (5). Asphyxia, severe infections, intracranial hemorrhage, trauma, hereditary mutations of the gene encoding arginine vasopressin and central nervous system malformations, may be the etiologic factors underlying neonatal CDI. In some rare cases no etiology can be found (6, 7). In a study conducted with 12 babies diagnosed with CDI during a ten-year period, it was reported that 10 babies had central nervous system malformations whereas only one patient had semilobar holoprosencephaly and partial corpus callosum agenesis similar to our patient (8). In another study including 23 babies diagnosed with CDI between

the ages of 1 day and 9 months, holoprosencephaly was found in 5 babies (9). Other studies reported perinatal asphyxia, intraventricular bleeding and idiopathic cases (10, 13). Considering the age at diagnosis of CDI in the literature, it was reported that CDI developed in the early neonatal period in two infants in one study and at the postnatal 90th day in another study (8, 9). In another case report, CDI developed on the postnatal 30th day in a baby diagnosed with holoprosencephaly (14). The age of the development of CDI was also in the late neonatal period in some other reports (11, 12). In our patient, intracranial hemorrhage, neonatal sepsis and meningitis were excluded, and CDI was accepted as secondary to HPE. Looking at the relationship between CDI and other endocrinopathies, no additional endocrinopathy was reported in some cases (9, 15), while anterior pituitary insufficiency accompanied HPE in other cases (8). In our patient, thyroid function tests (TSH, fT₄) and blood cortisol levels were normal excluding additional endocrinopathies. A standard treatment for neonatal CDI has not been defined in the literature and the management of these cases is difficult. It has been reported that intranasal desmopressin treatment causes hypernatremia and wide fluctuations in antidiuretic effects due to irregular nasal absorption in babies while oral desmopressin treatment has more positive results

than the intranasal route (11, 16, 17). Oral desmopressin treatment was preferred in our patient whose normal sodium levels were achieved with appropriate feeding and fluid support as needed.

In conclusion, although HPE is an uncommon condition, it should be kept in mind that hypernatremic dehydration may develop due to CDI in these patients, even in the early neonatal period. There is no predictive factor for the development of this condition to date, and close follow-up and management should be done accordingly.

Informed Consent: Written consent was obtained from the participants.

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REFERENCES

1. Dubourg C, Bendavid C, Pasquier L, Henry C, Odent S, David V. Holoprosencephaly. *Orphanet J Rare Dis* 2007;2:8. [CrossRef]
2. Makaryus AN, McFarlane SI. Diabetes insipidus: Diagnosis and treatment of a complex disease, review. *Cleveland Clin J Med* 2006;73(1):65-71. [CrossRef]
3. Dubourg C, Kim A, Watrin E, de Tayrac M, Odent S, David V, et al. Recent advances in understanding inheritance of holoprosencephaly. *Am J Med Genet* 2018;178(2):258-69. [CrossRef]
4. Barratt KS, Arkell RM. ZIC2 in Holoprosencephaly. *Adv Exp Med Biol* 2018;1046:269-99. [CrossRef]
5. Yang YH, Lin JJ, Hsia SH, Wu CT, Wang HS, Hung PC, et al. Central diabetes insipidus in children with acute brain insult. *Pediatr Neurol* 2011;45(6):377-80. [CrossRef]
6. Ferlin ML, Sales DS, Celini FP, Martinelli Junior CE. Central diabetes insipidus: alert for dehydration in very low birth weight infants during the neonatal period. A case report. *Sao Paulo Med J* 2015;133(1):60-3. [CrossRef]
7. Qureshi S, Galiveeti S, Bichet DG, Roth J. Diabetes insipidus: celebrating a century of vasopressin therapy. *Endocrinology* 2014;155(12):4605-21. [CrossRef]
8. Djermane A, Elmaleh M, Simon D, Poidvin A, Carel JC, Léger J. Central diabetes insipidus in infancy with or without hypothalamic adipsic hypernatremia syndrome: Early identification and outcome. *J Clin Endocrinol Metab* 2016;101(2):635-43. [CrossRef]
9. Kasim N, Bagga B, Diaz-Thomas A. Intracranial pathologies associated with central diabetes insipidus in infants. *J Pediatr Endocrinol Metab* 2018;31:951-8. [CrossRef]
10. Ueda H, Numoto S, Kakita H, Takeshita S, Muto D, Goto T, et al. Neonatal central diabetes insipidus caused by severe perinatal asphyxia. *Pediatr Ther* 2016; 6(1): 278. [CrossRef]
11. Atasay B, Berberoğlu M, Günlemez A, Evliyaoğlu O, Adıyaman P, Unal S, et al. Management of central diabetes insipidus with oral desmopressin in a premature neonate. *J Pediatr Endocrinol Metab* 2004;17(2):227-230. [CrossRef]
12. Yarber B, Wood B. Early diagnosis and treatment of diabetes insipidus in a newborn infant: a case study. *Neonatal Netw* 1992;11:17-20. PMID:1287448.
13. Quetin F, Garnier H, Brauner R, Vodovar M, Magny JF. [Persistent central diabetes insipidus in a very low birth weight infant] [Article in French]. *Arch Pediatr* 2007;14(11): 1321-3. [CrossRef]
14. Raisingani M, Gopi RP, Shah B. Use of chlorothiazide in the management of central diabetes insipidus in early infancy. *Case Rep Pediatr* 2017;2407028. [CrossRef]
15. Molnar Z, Sotiridou E, Dixon H, Ogilvy-Stuart A. Transient diabetes insipidus in a very-low-birthweight preterm infant with intraventricular haemorrhage. *Acta Paediatr* 2012;101(9):389-90. [CrossRef]
16. Fjellestad-Paulsen A, Paulsen O, d'Agay-Abensour L, Lundin S, Czernichow P. Central diabetes insipidus: Oral treatment with dDAVP. *Regul Pept* 1993;45(1-2):303-7. [CrossRef]
17. Stick SM, Betts PR. Oral desmopressin in neonatal diabetes insipidus. *Arch Dis Child* 1987;62(11):1177-8. [CrossRef]