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¹Shahid Beheshti University of Medical Sciences

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Abstract

Holoprosencephaly (HPE) is a complex brain malformation resulting from incomplete cleavage of the prosencephalon, occurring between the 18th and 28th day of gestation. Endocrinologic dysfunctions such as diabetes insipidus (DI), hypothyroidism, and growth hormone deficiency are common in HPE and correlated with the degree of hypothalamic non-separation.

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Difficult-to-treat Diabetes Insipidus in a Patient with Midline Defect: A Case Report

Atena Seifi^{1*}, Arefeh Zahmatkesh¹, Mahnaz Jamee¹, Mahbube Mirzaee¹, Masoumeh Mohkam¹

Pediatric Nephrology Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author(s):

Name:Atena Seifi

EmailAddress (Academic email address is):atenaseifi@sbmu.ac.ir

Phone No. (Available number for emergency calls):09107899668

ORCID ID: <https://orcid.org/0000-0002-9951-9317>

Abstract

Background

Holoprosencephaly (HPE) is a complex brain malformation resulting from incomplete cleavage of the prosencephalon, occurring between the 18th and 28th day of gestation. Endocrinologic dysfunctions such as diabetes insipidus (DI), hypothyroidism, and growth hormone deficiency are common in HPE and correlated with the degree of hypothalamic non-separation.

Case presentation

We reported a 5-month-old boy with median cleft lip and palate, with several episodes of myoclonic seizure and profound persisted hypernatremia. Magnetic resonance (MRI) revealed the septum pellucidum was

absent and HPE was reported. During laboratory investigation, his primary sodium level was 170 mmol/L and his urine specific gravity was 1003. based on these findings and clinical response to vasopressin, diagnosis of central diabetes insipidus was made.

Conclusion

In case of midline defects accompany by hypernatremia, seizures, polyuria with or without developmental delay, the brain should be imaged to confirm its morphology and investigation of associated endocrinologic dysfunctions should be suspected.

Keywords : Diabetes Insipidus, Cleft lip, Cleft palate, Midline defect, Holoprosencephaly

List of abbreviations:

DI: Diabetes Insipidus

CDI: Central Diabetes Insipidus

HPE: Holoprosencephaly

MRI: Magnetic Resonance Imaging

ADH: Anti Diuretic Hormone

aDAVP: Desmopressine

PFO: Patent Foramen Ovale

PDA: Patent Ductus Arteriosus

VSD: Ventricular Septal Defect

AVP: Arginin-Vasopressin

I. Introduction

Holoprosencephaly (HPE) is a relatively rare developmental defect in the median structures of the brain and face that results from impaired cleavage of the embryonic forebrain. HPE occurs in 5–12/10,000 live births (1), whereas an estimated 40 per 10 000 cases are seen among human abortions indicating a high rate of fetal loss (2).

Patients with holoprosencephaly frequently display craniofacial anomalies including midline facial clefts, cyclopia and nasal anomalies. , They may also suffer from dysfunctions in the pituitary glands presenting with diabetes insipidus (3).

Holoprosencephaly is etiologically diverse and can be perturbed by both genetic and environmental causes, either individually or more likely in combination with other congenital disorders. Approximately 65% of holoprosencephaly appears to be sporadic and cannot be ascribed to any known cause. Clinically, there is a nearly continuous spectrum of malformations consistent with HPE which can manifest with variable expressivity and/or penetrance, demonstrated by the segregation analysis of familial cases (4).

Patients manifest a wide spectrum of clinical conditions and neurologic dysfunction. Severity of symptoms correlates with the degree of hemispheric nonseparation (5). Because the clinical spectrum of this defect has been inadequately described in milder forms, we aim to report an Iranian patient with holoprosencephaly with associated DI, which was found to be refractory to conventional treatments.

II. Case Presentation

The index patient was a 5-month-old male infant, born to non-consanguineous healthy parents. He was the second child of the family and his female sibling was healthy. No history of abortion, early death, or prenatal abnormality was reported.)**Figure.1**)

The baby was born post-term (at 40 weeks of gestation) through vaginal delivery with a birth weight of 3500 grams. At birth, the cleft lip and palate were diagnosed, and he was admitted to the neonatal ward for 24 hours to practice sucking under health care team observation. The physical examination was otherwise normal. He was PO tolerant and was discharged on the second day of birth with personal permission.

He was screened for the presence of accompanying anomalies by the ultrasound of the brain, heart, abdomen, and pelvis, which revealed normal results except for patent foramen ovale (PFO) and a small patent ductus arteriosus (PDA). (**Figure.2 (A-C)**)

The mother states that the number of diapers that became completely heavy from birth was about 7-8 diapers per day. The infant had no problem thereafter and had a normal weight gain. At the fourth month of age, the mother noticed episodes of myoclonic (UWG) movements lasting for a few seconds about 2 to 3 times during daytime and when falling asleep. The frequency of these attacks gradually increased, and limbs spasm was added on. During an outpatient visit to a pediatric neurologist, the primidone (Liskantin®) is started, and he was recommended to return if there was no response to treatment. The levetiracetam was added after a week due to the continued seizure attacks, with no significant response, and the infant was admitted to the Qom Shohada Hospital. In the spiral brain computed tomography (CT) the septal agenesis was suspected and in the magnetic resonance imaging (MRI), the septum pellucidum was absent and holoprosencephaly was reported. The electroencephalogram (EEG) was abnormal. In addition, the serum sodium level was above the normal range (Na: 169 meq/L). During his two-week admission, the number of seizure episodes declined but the hyponatremia did not resolve.

Due to his refractory hyponatremia, he was referred to the Mofid Children's Hospital and the nephrology and neurology services were consulted. Upon admission to this center, he had fever and hyponatremia (Na: 170 meq/L). The maintenance serum (1.2 L) was placed for the patient and the paraclinical workup was performed to rule out infectious etiologies (including COVID-19 PCR), all of which were negative. On the second day of hospitalization, according to the low urine specific gravity (SG: 1003) and high serum sodium level (Na: 169 meq/L), he was diagnosed with diabetes insipidus (DI). With the serum sodium of 145 meq/L, he received a puff of DDAVP spray equivalent to 10 micrograms of desmopressin, while on cardiac monitoring and vital signs check. The serum sodium reached 131 meq/L two hours after receiving desmopressin and 118 meq/L four hours later, and the urine SG reached 1011. The patient developed seizures, controlled by hypertonic sodium and diazepam. Three days later, the patient's condition stabilized and he was re-initiated on desmopressin spray, diluted in a proportion of 1:4. There was no change in plasma sodium and urine SG levels. The next day, with a serum sodium level of 144 meq/L, a two-fold dose of desmopressin (1:2 concentration) was administered which resulted in a sodium drop to 134 meq/L, 2 hours later, and 119 meq/L, 4 hours later, with urine SG of 1015. and received hypertonic sodium again. In the re-administration of a quarter dose with serum sodium of 154 meq/L, this time, he experienced a decrease in sodium by 102, 2 hours after receiving desmopressin, the urine SG reached 1015, and urine volume decreased subsequently. The desmopressin was discontinued and no hyponatremia was detected during the follow-up.

III. Discussion

Central diabetes insipidus (CDI) is a complex disorder characterized by excretion a large volume of dilute urine due to the defective production, transport, or secretion of arginine-vasopressin (AVP). This condition is mainly caused by hypothalamus dysfunction. polyuria, defined as urine volume $> 2 \text{ L/m}^2/24\text{h}$ 150 mL/kg/24h at birth, 100-110 mL/kg/24h up to 2 years of age, and 40-50 mL/kg/24h in older children and adult (6), occurs when more than 80-90% of AVP-secreting neurons found in supraoptic and paraventricular nuclei are damaged (7).

Congenital CDI is observed mainly in a neonate with brain malformations including inclusive of optic nerve hypoplasia, septo-optic dysplasia, HPE, and absence of the internal carotid. Moreover, CDI has been found in children and adolescents in the presence of inflammatory/autoimmune conditions, Langerhans histiocytosis (LCH), intracranial germ cell tumors, infectious, vascular disease, trauma, and sellar surgery as acquired etiologies (8).

HPE spectrum disorders, resulting from failed forebrain deviation observed in cases with midline brain malformation include corpus callosum agenesis, absent septum pellucidum, absent olfactory bulbs and tracts, and vermillion hypoplasia. Associated findings with HPE include craniofacial dimorphism, neurologic issue, feeding problems, and endocrinopathies (9). It is etiologically heterogeneous and may be caused by maternal ingestion of massive doses of salicylate, maternal diabetes, poverty, and parental exposure to cytomegalovirus (8). Midline facial anomalies are typically related to the severity of the brain malformation (10). Olsen et al described eye malformation in 76.8% of patients, nose malformation in 69.5%, ear malformations in 50%, and oral cleft in 41.5%. These malformations arise at different stages during gestations (11).

A study on 68 patients with HPE showed 33 of 68 (49%) patients had at least one seizure, without a direct relationship with seizure prevalence and severity of HPE. In addition, 49 (72%) patients had at least a sodium balance problem in the form of DI (12). On the other hand, medical reports of 117 children with HPE by Hahn et al shows seizure are often present (13). Neurologic examination on a case of HPE revealed microcephaly with spastic quadriplegia (14).

In our case study early heart evaluation by echocardiography, revealed some structural defects as patent foramen oval (PFO) and patent ductus arteriosus (PDA). Comorbidity of HPE and congenital heart disease (CHD) in an individual with genetic variants in known HPE-related genes has been recently observed. Cardiac assessment in 434 individuals with HPE, showed 8% (n=33) identified CHD. 4 of 33 cases (12%) included PFO and two of these four cases of PFO had the finding of PDA.(15). more than any other birth anomalies, CHD is in communication with numerous genetic conditions. PDA in association with ventricular septal defects (VSD) and aortic coarctation, reported the most common cardiac anomalies in a case of Edward syndrome with central diabetes insipidus (16).

In our case study, polyuria provided an important clue for the diagnosis. In most cases of CDI, primary symptoms are persistence polyuria and polydipsia, young children may have severe dehydration, vomiting, constipation, fever, irritability, sleep disturbance, nocturia, failure to thrive, and growth retardation. Another prominent sign in our case was seizures, which may be caused due to hypernatremia or HPE-related (6). Investigation of CDI can be straightforward but underestimated polyuria by parents and poor accuracy of the biochemical test can lead to delayed diagnosis and incorrect management. when polyuria is confirmed, urinary osmolality measurement would be the second step. A random urine osmolality >700-900 milliosm/kg indicates the appropriate renal response to endogenous vasopressin, thereafter, in whom urine osmolality of <700-800 milliosm /kg, serum sodium (>143 mmol/kg) and plasma osmolality measurement could be suggestive of DI. The next investigation in water drinker patients with normal or low serum sodium is the water deprivation test and desmopressin (DDAVP) challenge. The administration of 5-10 µg of desmopressin intranasal will help differentiate CDI from NDI. A case report in 2018 shows intravenous vasopressin as a safe way to diagnosing neonatal CDI.3 for the first time.(17) Recently, Copeptin, the c-terminal segment of AVP precursor peptide, become available as an attractive new surrogate marker for diagnosis of DI (18). As germinoma is a tumor-inducing CDI, germ cell tumor markers can be useful for the early diagnosis of CDI (19). In addition, early signs of polyuria (heavy diaper) and refractory hypernatremia, in our study, DI diagnosis was based on high serum sodium level and low urine specific gravity and CDI confirmed by the effect of dDAVP on decreasing serum sodium levels.

It is important to note that the index patient progressed to hyponatremia soon after initiation of desmopressin. After discontinuation of desmopressin and adjustment of serum therapy, she no longer experienced remarkable changes in serum sodium level. This sudden progression to hyponatremia after administration of desmopressin may be explained by resetting of the osmostat. This condition is due to chronic effect of volume expansion on ADH release, as a result of which, a higher osmolality is recognized as normal (20, 21).

Primary imaging study due to persistent seizures made our differential diagnoses narrower, with CDI related to HPE. Magnetic resonance imaging (MRI) is a crucial neuroimaging for CDI and is a primary method for evaluating the sellar/suprasellar region with high contrast resolution and lack of invasiveness in pediatric patients with CDI. We can use computed tomography (CT) for providing complementary information when a detailed assessment of bone involvement is required (22).

The cardinal treatment approach for CDI is free access to water associated with a pharmacologic agent, Desmopressin. Desmopressin (dDAVP) is a synthetic AVP analog, administered orally, intranasally, or parenterally (23). Daily dosages for oral preparations (20-fold less potent than the intranasal form) vary from 100 to 1200 g in three doses, for the intranasal preparations, approximately 2.5-40 g (once or twice a day) and for parenteral use, a low dose should be used initially and increased as necessary. The intranasal formulation remains of benefit in patients that need an individualized administration of the dose (23, 24).

The management of CDI in infancy is very challenging because of different individual responses and limited treatment options (25). Furthermore, ML Moritz and JC Ayus demonstrate that hypernatremia is in combination with a 15% mortality rate in children, which is estimated 15 times higher than the age-matched mortality in hospitalized children without hypernatremia (26). In a study on 4 cases of CDI (one of them was HPE), several episodes of hyponatremia (serum sodium < 130 mmol/L) and hypernatremia (serum sodium > 150 mmol/L) were reported. Their results pointed that a combination of hydrochlorothiazide (HCTZ) with low solute feed resulted in less alteration in serum sodium than desmopressin (25, 27). The mechanism of HCTZ is not exactly known, several hypotheses suggest that after increased renal sodium excretion, extracellular volume contraction leads to decreased GFR and increased tubular sodium and water reabsorptions. In addition, renal solute load, point to all solutes of exogenous or dietary origin that require excretion by the kidney, help to decrease urine output (25). Limited researches report other treatment options in CDI with different mechanisms, like Carbamazepine, Chlorpropamide and Indapamide (28).

Danielle C.M et al demonstrated the challenges in a case of CDI; as they started intranasal desmopressin (0.2 ug/kg), oliguria several hours of anuria and a 25-point drop in sodium level within 15 hrs was ensued. Rapid reduction of hypernatremia can cause significant mortality and morbidity. This study recommends using low dose of intranasal desmopressin (0.05-0.1 ug/kg) if oral desmopressin is not well tolerated and also emphasizes the importance of dose titrations based on clinical and biochemical response (29). In our study, a persistent seizure occurred prior to CDI diagnosis. However, tonic-clonic movement and other neurological sequela were related to hypernatremia. It makes sense that electrolyte evaluation based on physical examinations (cleft lip and palate with polyuria) can help us to apply the best management.

Declarations:

Ethics approval and consent to participate: Informed consent was obtained from the patient and parents of the patient prior to being included in the study.

Consent for publication: Written consent for publication was taken from the patient and his parents.

Availability of data and materials: Not applicable.

Competing interests: The authors declare that they have no conflict of interest.

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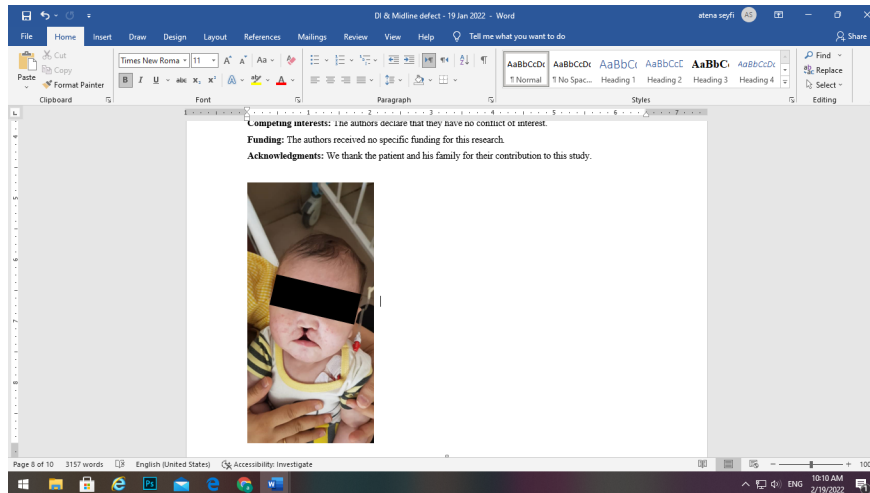


Figure 1. Cleft lip and palate in the index patient.

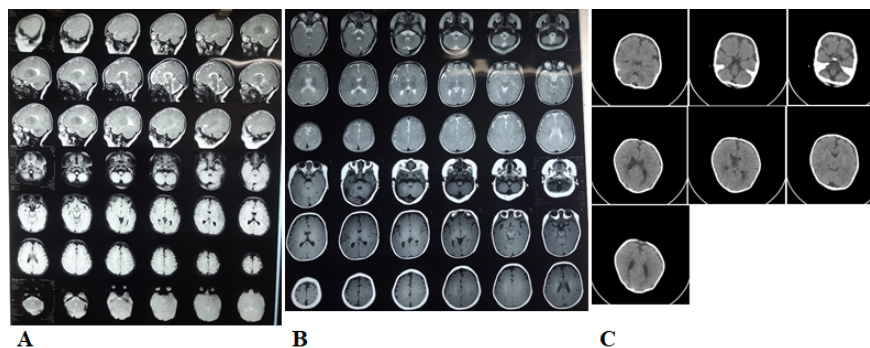


Figure.2 (A-C). Holoprosencephaly in brain CT scans. Brain parenchyma has normal density and septal agenesis is suspected. Ventricular system is normal and no mass effect or midline shift is observed in supra- and infra-tentorial region. Posterior fossa, cerebellopontine angle, pons, and midbrain are unremarkable. No hemorrhage or calcification is evident.

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