

Semilobar Holoprosencephaly with Neurogenic Hypernatraemia

Two new cases

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إندماج مقدّم الدماغ نصف الفصي مع زيادة صوديوم الدم العصبي المنشأ

حالتان جديدتان

هاشم جافاد، سيف اليعروبي، الكسندر شاكو، ديليب سانكلا، أمنه الفطيسي، أنس الوجود عبد المغيث، محمد النجاري

المخلص: اندماج مقدّم الدماغ نصف الفصي (HPE) هو عيب النمو في مقدمة المخ الجنيني ومنتصف الوجه. ذلك يرجع إلى عدم انقسام مقدّم الدماغ الجنيني إلى نصفي الكرة المخية والتطور غير المكتمل للأجزاء المجاورة للناصف. يصل معدل أنتشار الي 1.31 لكل 10,000 ولادة. يمكن أن تكون مسببات المرض وراثية، بيئية، أو كليهما. يصنف HPE إلى فصي، نصف فصي، لا فصي وأنواع فرعية أخرى بناء على درجة انفصال نصفي الكرة المخية. نحن نقدم تقريراً عن حالتين جديدتين مصابين باندماج مقدّم الدماغ نصف الفصي مع زيادة صوديوم الدم العصبي المنشأ. يعتبر نقص الأحساس بالعطش المرتبط بزيادة صوديوم الدم المزمن في المرضى الذين يعانون من اندماج مقدّم الدماغ نصف الفصي مؤشراً قوياً على وجود "زيادة صوديوم الدم العصبي المنشأ". التعرف المبكر على زيادة صوديوم الدم العصبي المنشأ مهم لأنه يتحسن مع العلاج القسري بالسوائل ولا يتطلب أي دواء.

مفتاح الكلمات: اندماج مقدّم الدماغ، نصف الفصي، زيادة صوديوم الدم، عصبي المنشأ، نقص الأحساس بالعطش، الناصف، تشوهات، تقرير حالة، عمان.

ABSTRACT: Holoprosencephaly (HPE) is a developmental defect of the embryonic forebrain and midface. It is due to the non-cleavage of the embryonic forebrain into two cerebral hemispheres and the incomplete development of the paramedian structures. The overall prevalence is 1.31 per 10,000 births. The aetiology could be genetic, environmental, or both. HPE is classified into alobar, semilobar, and lobar subtypes based on the degree of separation of the cerebral hemispheres. We report two new cases of semilobar HPE with neurogenic hypernatraemia. Lack of thirst and hypodipsia associated with chronic hypernatraemia in patients with HPE is highly suggestive of neurogenic hypernatraemia. Early identification of neurogenic hypernatraemia is important as it improves with forced fluid therapy and does not require any medication.

Keywords: Holoprosencephaly; Semilobar Holoprosencephaly; Hypernatremia, neurogenic; Hypodipsia; Midline; Malformations; Case Report; Oman.

WE REPORT TWO NEW CASES OF semi lobar holoprosencephaly (HPE) complicated by neurogenic hypernatraemia without signs of dehydration.

Case One

A two-year-old female first presented at the age of one year with global developmental delay. She is the sixth child of consanguineous parents. She was born normally after an uneventful pregnancy and had good Apgar scores. Anthropometric parameters

were suggestive of intrauterine growth restriction (IUGR). She was discharged on the second postnatal day. At the age of 10 months, she was evaluated in a peripheral hospital for delayed growth and development, and investigations revealed persistent hypernatraemia. She was referred to Sultan Qaboos University Hospital (SQUH), Muscat, Oman, for further evaluation of hypernatraemia and developmental delay. There was no history of excessive fluid loss or high salt intake. On examination, her vital signs were stable and there were no signs of significant dehydration. All her

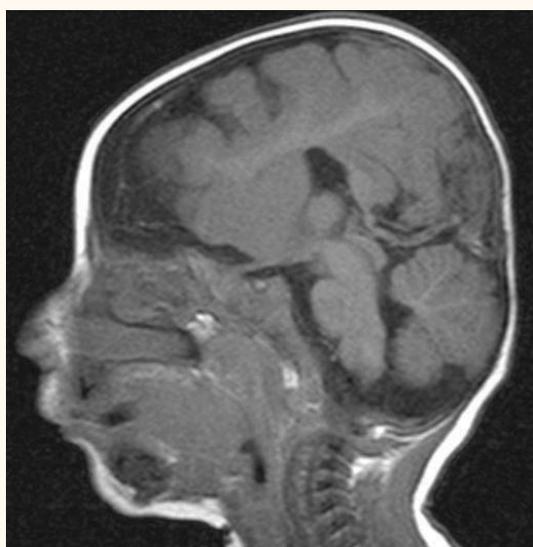


Figure 1: Sagittal T1 fluid attenuation inversion recovery (FLAIR) image shows *corpus callosum* dysgenesis and hypoplasia of the frontal lobe with thick gyri.

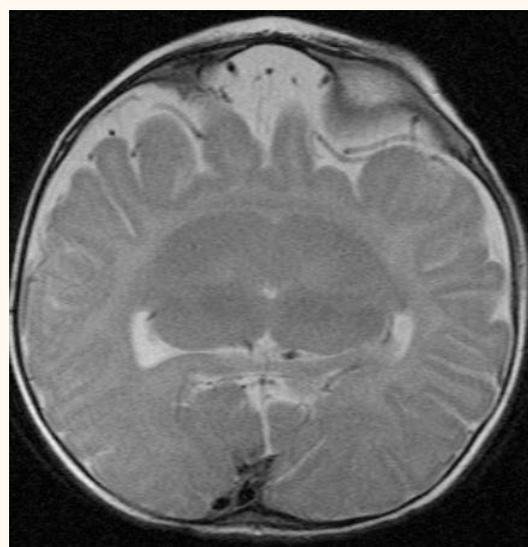


Figure 1: Axial T2WI magnetic resonance image shows fused basal nuclei, absent *septum pellucidum*, and a small third ventricle.

growth parameters were below the third percentile, with a developmental age of 2 to 3 months. She had dysmorphic features (i.e. microcephaly, closely spaced eyes, and depressed infantile nose and synophrys). A neurological examination revealed microcephaly with spastic quadriplegia. Other systemic examinations were unremarkable.

A blood work-up revealed persistent hyponatraemia (159–167 mmol/L). Renal functions were normal (serum urea: 3.4–7 mmol/L; creatinine: 18–25 $\mu\text{mol/L}$). The serum biochemistry revealed potassium levels at 4.1–4.4 mmol/L, chloride at 126–131 mmol/L, bicarbonate at 24–28 mmol/L, and the anion gap ranging from 11–13 mmol/L.

Her plasma anti-diuretic hormone (ADH) level was low (<0.5 pmol/L) for the serum osmolality (331 mmol/Kg). There was no change in urine osmolality following subcutaneous administration via injection of desmopressin. Urine osmolality before and after desmopressin administration was almost the same, at 300 mmol/Kg. A serum hormonal assay revealed a cortisol level of 301 nmol/L at 9 am (range: 185–624), a T4 level of 15.1 pmol/L, a thyroid stimulating hormone level of 1.96 μL , and growth hormone levels at 3.88 μL (range: 0.01–3.60 μL). Urine output was 4–4.5 ml/Kg/hr.

A magnetic resonance imaging (MRI) brain scan revealed a partially-formed inter-hemispheric fissure situated posteriorly. The frontal lobes were fused, but the *thalami* were partially separated.

There was a single lateral ventricle with indication of the third ventricle. The *corpus callosum* was partially formed with normal orbits and optic nerves. There was a large posterior cranial fossa cystic lesion. These findings were consistent with semilobar HPE [Figure 1].

The infant was not thirsty and did not demand feeding. She required nasogastric tube feeding to maintain a normal hydration level as her parents refused a gastrostomy. She is currently undergoing regular follow-up and, with fluid management, her serum sodium levels have been maintained at levels between 142–148 mmol/l for the last year. There have been no complications of hyponatraemia, and she is undergoing physiotherapy for her spasticity.

Case Two

An 8-month-old male infant born normally was admitted for evaluation of stridor, microcephaly and developmental delay. An examination revealed tachycardia and tachypnoea with normal temperature and blood pressure. As in the first case, the infant was not thirsty and did not demand feeding. Hydration status and urine output were satisfactory. All growth parameters were below the third percentile. Dysmorphic features like microcephaly, depressed infantile nose and closely spaced eyes were obvious. The serum biochemistry revealed persistent hyponatraemia (152–164 mmol/L). Renal functions were normal (serum creatinine: 28 $\mu\text{mol/L}$). There was hypodipsia even

when the serum osmolality was above 310 mmol/Kg. The serum electrolytes, urine and serum osmolality were similar to the first case. There were no associated endocrinopathies like hypothyroidism, hypocorticism or growth hormone deficiency. There was no change in the urine osmolality following administration of desmopressin. A serum ADH level assessment was not requested in the second case as the history, dysmorphic features, and investigations were suggestive of semilobar HPE associated with neurogenic hypernatraemia. An MRI brain scan revealed normal-sized third ventricles in the midline. Both lateral ventricles are fused across the midline as a monoventricle. The *thalami*, the heads of the caudate *nuclei*, and the frontal lobes are also fused across the midline with an absent *falx cerebri* and an interhemispheric fissure consistent with semilobar HPE [Figure 2].

The infant was managed with nasogastric feeds as the parents were not willing for the baby to undergo a gastrostomy. The hypernatraemia improved with appropriate fluid management (serum sodium: 144–147 mmol). The child is undergoing regular follow-up, gaining weight and undergoing physiotherapy for spasticity.

Discussion

HPE is a developmental defect caused by the failure of the *prosencephalon* (the embryonic forebrain) to divide into the two lobes of the cerebral hemispheres. The incidence is 1.31 per 100,000 live births.¹ The aetiology can be genetic, environmental, or both.² Numerous genes have been linked to HPE, including *sonic hedgehog*, *ZIG2*, *SIX3*, *TGIF*, and others.³ Environmental factors, such as maternal diabetes, retinoic acid, and drugs and alcohol abuse during early pregnancy have also been implicated.^{4,5} Chromosomal anomalies like trisomy-13 18p-deletion, 13p-deletion, and the Meckel-Gruber syndrome can be associated with HPE.⁶ The defect is also associated with chromosomes 2, 3, 7, 13 and 18.

De Myer divided HPE into three categories: alobar, semilobar and lobar, depending upon the severity of the defect.⁷ Alobar is the most severe form, marked by the formation of only one cerebral hemisphere and one ventricle.⁸ The semilobar and lobar forms may be associated with mild facial dysmorphism, like abnormal upper labial

frenulum, the formation of just a single incisor or a cleft palate.^{7–10} Lobar HPE usually presents with developmental delay, and/or hypothalamic and pituitary dysfunctions.

The distinction between semilobar and lobar HPE is poorly defined.⁷ HPE is frequently associated with endocrinopathies such as *diabetes insipidus*, hypocorticism, hypothyroidism and growth hormone deficiency because of midline defects.¹¹ Seizures may occur. There are reports of neurogenic hypernatraemia associated with HPE.¹¹

Neurogenic hypernatraemia is a rare complication of semilobar HPE. The commonest cause of hypernatraemia in HPE is central *diabetes insipidus*, which occurs in 70% of patients with classic HPE.¹¹ Neurogenic hypernatraemia is marked by a defective thirst mechanism, either alone or in combination with impaired osmoregulation and ADH release.¹¹ It is characterised by chronic hypernatraemia with adipsia, or hypodipsia polyuria with no sign of dehydration. In *diabetes insipidus*, hypernatraemia is associated with polydipsia, polyuria, and signs of dehydration.^{8,12,13}

A central osmoregulatory defect is due to hypodipsia with normal levels of serum ADH, even if there is plasmatic increase in osmolality.^{14,15} These findings suggest that HPE may be associated with a defect in the hypothalamic osmoreceptors that control thirst and vasopressin secretion, probably due to a defect of embryonic development.

Both of our cases had dysmorphic features such as closely-spaced eyes, a depressed infantile nose, synophrys, microcephaly and spastic quadriplegia; all of these are suggestive of a structural anomaly of the brain. MRI brain scan findings were consistent with semilobar HPE in both of these cases.

Chronic hypernatraemia without signs of dehydration is usually seen in patients with neurogenic hypernatraemia. This is similar to the findings in our patients. Causes of hypernatraemia, like excessive fluid loss and increased salt intake, were excluded in both patients. There were no vascular, neoplastic or degenerative causes for chronic hypernatraemia in either patient. Neither of them was thirsty at all, even when their serum osmolality levels were high (≥ 331 mmol/Kg). Serum ADH was only done in the first patient and it was within the normal reference range (< 0.5 pmol/L), but was low for the serum osmolality (331 mmol/Kg). This can be explained by the disturbance of

the hypothalamic osmoreceptors, which govern vasopressin as seen in patients with neurogenic hypernatraemia.¹² There was no change in either patient in urine osmolality upon the exogenous administration of desmopressin, ruling out central *diabetes insipidus*. Low serum ADH levels and normal renal functions, as observed in the first patient, are counter-indicative of nephrogenic *diabetes insipidus*. In nephrogenic *diabetes insipidus*, the serum ADH levels are usually high.

In spite of extensive investigations, a definite aetiology for hypernatraemia other than neurogenic hypernatraemia was not detected in our patients. The chronic hypernatraemia in both patients improved with forced nasogastric feeds, as has been observed in other cases of neurogenic hypernatraemia. Both patients are now gaining weight and maintaining acceptable serum sodium levels with proper hydration, which also rules in favour of neurogenic hypernatraemia.

Conclusion

In children with HPE, chronic hypernatraemia is usually due to central *diabetes insipidus*. Neurogenic hypernatraemia should be considered in children with HPE presenting with chronic hypernatraemia without signs of dehydration, and who lack thirst and have adipsia. It improves with fluid management as the defect is in the central osmoregulation. The association of HPE with central *diabetes insipidus* has to be considered in all cases of HPE with chronic hypernatraemia, as it is the commonest cause. The presence of thirst, a poor response to fluid management alone, and an improvement with desmopressin would rule in favour of central *diabetes insipidus*, whereas the reverse is true for neurogenic hypernatraemia. Early identification and management of neurogenic hypernatraemia with appropriate fluid management avoids extensive investigations and complications secondary to exogenously-administered ADH.

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