

Neonatal Central Diabetes Insipidus Caused by Severe Perinatal Asphyxia

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Rec date: Feb 10, 2016, Acc date: Feb 25, 2016, Pub date: Feb 29, 2016

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Abstract

We describe three rare cases of neonatal central diabetes insipidus (CDI) caused by severe perinatal asphyxia. In these cases, hypernatremia, high plasma osmolality and hyposthenuria, with polyuria occurred after one week of age. CDI in one case might be due to the temporal dysfunction of hypothalamic-neurohypophyseal axis and the other two cases to permanent dysfunction. Although these cases are rare, early diagnosis and treatment of CDI are indispensable. Follow-up of serum sodium, serum and urine osmolality is necessary after acute phase to maintain water and electrolyte homeostasis in severe perinatal asphyxia.

Keywords: Central diabetes insipidus; Desmopressin; Hypoxic ischemic encephalopathy; Perinatal asphyxia; Anti-diuretic hormone

Introduction

Central diabetes insipidus (CDI) is the result of a deficiency of anti-diuretic hormone (ADH) due to dysfunction of the posterior pituitary and/or hypothalamus [1,2]. CDI is an uncommon disorder characterized by polyuria, hypernatremia, high plasma osmolality, and low urine osmolality. Water and electrolyte homeostasis in newborns is affected by postnatal physiological adaptation, and appropriate management is important, especially for the seriously ill newborn. Dehydration with hypernatremia can occur, associated with insensible water loss, high urine output, and reduced ability to secrete sodium in neonatal CDI cases [1,2]. Therefore, careful monitoring is needed to maintain water and electrolyte balance in neonatal CDI. CDI can result from various etiologies, including central nervous system malformation, inflammation, trauma, infection, intracranial hemorrhage, dehydration, hypoxia, and inherited mutations of the gene encoding for arginine vasopressin [3-5].

Perinatal asphyxia is associated with multi-organ hypoxia-ischemia and subsequent dysfunction, and it may be caused by perinatal events, such as maternal or fetal hemorrhage, intermittent or acute umbilical cord compression, uterine rupture, placental abruption, or shoulder dystocia, affecting the supply of oxygenated blood to the fetus [6]. Some cases of perinatal asphyxia develop hypoxic ischemic encephalopathy (HIE) and multiple organ impairment, such as disseminated intravascular coagulation and respiratory, liver, heart, and renal failure [6]. Although perinatal asphyxia could potentially lead to CDI, CDI caused by severe asphyxia is very rare. We encountered three cases of neonatal CDI caused by severe perinatal asphyxia in our NICU for five years.

Case Reports

Case 1

A 2765-g male was born at a gestational age of 39 weeks and 6 days by emergency caesarean section following fetal bradycardia. His mother was a primipara at 30 years old and did not have any problem in her pregnancy progress. His Apgar score was 1 at 1 min and 4 at 5 min. The infant was intubated immediately after birth. On initial physical examination, he was comatose, with severe hypotonia and failure to maintain spontaneous respiration. In addition, severe metabolic acidosis (arterial blood: pH 6.692, PaCO₂ 59.4 mmHg, base excess -29 meq/l, HCO₃ - 7.2 mmol/l), and a burst suppression pattern in the amplitude-integrated EEG (a-EEG) indicated severe or moderate HIE. His neurological symptoms did not improve, and effective spontaneous breathing did not appear after therapeutic hypothermia for 72 hours from five hours after birth. Head computed tomography at 10 days revealed diffuse white matter damage and basal ganglia and thalamus damage consistent with severe HIE. We did not check head MRI because we thought there was little information to be provided much more.

Laboratory examinations at 13 days of age revealed hypernatremia (161.3 mmol/l, normal range: 135-145 mmol/l), high plasma osmolality (337 mOsm/kg, normal range: 276-292 mOsm/kg), and hyposthenuria (70 mOsm/kg, normal range: 40-1400 mOsm/kg), with polyuria (7.8 ml/kg/h). Though the plasma ADH level was not measured, these laboratory data and rapid recovery (serum sodium 129 mmol/l, plasma osmolality 272 mOsm/kg, and urine osmolality 290 mOsm/kg) after intranasal desmopressin (0.125 µg) led to the diagnosis of CDI. After adjusting the dosage of desmopressin, the serum sodium level stabilized. The desmopressin was necessary until he died of respiratory disorder due to aspiration-related pneumonia at 11 months. Other than central hypothyroidism, clinical findings to suggest other endocrine dysfunctions, including hypoglycemia and failure to grow normally, were not seen.

Case 2

A 2610-g male at a gestational age of 35 weeks and 5 days and Apgar score 1 at 1 min and 4 at 5 min, was born by emergency caesarean section with abruptio placentae. His mother was a primipara at 28 years old and did not have any problem in her pregnancy progress. The infant was intubated immediately after birth. On initial physical examination, he was comatose with severe hypotonia and failure to maintain spontaneous respiration. Laboratory examinations showed metabolic acidosis (venous blood: pH 7.123, PaCO₂ 63.7 mmHg, base excess -8.8 meq/l, HCO₃ - 20.4 mmol/l). The a-EEG showed a continuous low voltage pattern. He was excluded from therapeutic hypothermia because of preterm birth. Despite intensive care, effective spontaneous breathing did not appear. Head MRI at 12 days revealed diffuse white matter damage and basal ganglia and thalamus damage consistent with severe HIE, but normal posterior pituitary intensity. A gradual increase of serum sodium levels led to hypernatremia (160 mmol/l), high plasma osmolality (333 mOsm/kg), hyposthenuria (149 mOsm/kg), polyuria (6.3 ml/kg/h), and a relatively low level of plasma ADH (2.7 pg/ml, normal range:0.3-3.5pg/ml) at 31 days of age. These findings led to the diagnosis of CDI. At 39 days of age, intranasal desmopressin was started at a dosage of 0.6 µg. After adjusting the dosage of desmopressin, the hypernatremia and hyposthenuria improved (serum sodium 136 mmol/l, urine osmotic pressure 268 mOsm/kg) at 45 days of age. The desmopressin was necessary until he died of respiratory disorder due to aspiration-related pneumonia at 5 months. Clinical findings to suggest other endocrine dysfunctions, including hypoglycemia and failure to grow normally, were not seen.

Case 3

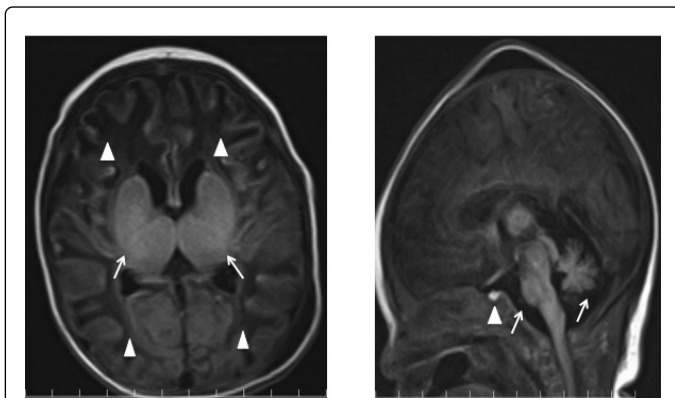


Figure 1: MRI findings in case 3 at 12 days of age. (Left: Axial T1-weighted image, Arrowhead: Diffuse white matter damage, Arrow: Basal ganglia and thalamus damage, Right: Sagittal T1-weighted image, Arrowhead: Normal posterior pituitary intensity, Arrow: Atrophy of the cerebellum and brainstem).

A 3149-g girl was born at a gestational age of 41 weeks and 4 days by emergency caesarean section following fetal bradycardia. Her mother was a primipara at 32 years old and did not have any problem in her pregnancy progress. Her Apgar score was 0 at 1 min, 0 at 5 min and 5 at 10 min. The infant was intubated immediately after birth, followed by endotracheal administration of adrenalin. On initial physical examination, she was comatose, with severe hypotonia and failure to maintain spontaneous respiration. In addition, severe metabolic acidosis (venous blood: pH 6.514, PaCO₂ 64.4 mmHg, base

excess -37.2 meq/l, HCO₃ - 5.4 mmol/l), and a continuous low voltage pattern on the a-EEG indicated severe HIE. Her neurological symptoms did not improve, and effective spontaneous breathing did not appear after therapeutic hypothermia for 72 hours from five hours after birth. Head MRI at 12 days of age showed diffuse white matter damage, basal ganglia and thalamus damage, and atrophy of the cerebellum and brainstem consistent with severe HIE, but normal posterior pituitary intensity (Figure 1). A gradual increase of serum sodium led to hypernatremia (151 mmol/l), high plasma osmolality (318 mOsm/kg), hyposthenuria (70 mOsm/kg), polyuria (6.1 ml/kg/h), and a relatively low level of plasma ADH (0.8 pg/ml) at 13 days of age. These findings led to the diagnosis of CDI. After 16 days of age, the serum sodium level reached and maintained normal levels without desmopressin. Clinical findings to suggest other endocrine dysfunctions, including hypoglycemia and failure to grow normally, were not seen.

Discussion

CDI is an uncommon disorder characterized by hypernatremia, hyposthenuria, and polyuria due to a deficiency of ADH from the posterior pituitary, especially in newborn. Although hypernatremia is seen if fluids replacement is lacking, our cases had appropriate infusion management. CDI occurs in patients with overwhelming central nervous system injuries, and may be associated with brain death [3]. In neonate, CDI has been described as a complication of intrauterine and perinatal disease [3,4]. Some authors have suggested that possible causes of CDI may include asphyxia, severe infections, peri or intraventricular hemorrhage, and central nervous system abnormalities [1,2,4]. The state that is almost brain death caused by the severe perinatal asphyxia might develop in CDI. There should be more CDI cases caused by severe perinatal asphyxia and are not only recognized, because severe perinatal asphyxia does not often become a target of the aggressive diagnosis and treatment. However, to the best of our knowledge, there are a few reports of neonatal CDI caused by severe perinatal asphyxia [7]. Khare et al. reported one case of neurohypophyseal dysfunction following perinatal asphyxia. Although progress of their case was the same as ours, they did not have the detailed examination including head MRI and measurement of plasma ADH [7].

Perinatal asphyxia is defined as oxygen deprivation that occurs around the time of birth caused by maternal or fetal hemorrhage, intermittent or acute umbilical cord compression, uterine rupture, or shoulder dystocia affecting the supply of oxygenated blood to the fetus. Perinatal asphyxia affects some four million neonates worldwide each year, causing the death of one million of them [8]. In most cases, the infants successfully recover from the hypoxic condition, but some patients develop HIE, leading to permanent neurological sequelae, such as seizure disorders, cerebral palsy, cognitive delays, and motor disabilities [6]. Furthermore, in addition to neurologic failure, asphyxia could lead to multiple organ impairment (central nervous system 28%, cardiovascular system 25%, kidneys 50%, and lungs 23%) [9,10]. Clinical findings, laboratory examination, aEEG, and MRI in the present three cases showed severe perinatal asphyxia. Despite intensive care and therapeutic hypothermia (except case 2), their neurological symptoms did not improve, and effective spontaneous breathing did not appear.

CDI was diagnosed by the presence of hypernatremia (>150 mmol), high plasma osmolality (>300 mOsm), low urine osmolality (<300 mOsm/l), low plasma ADH levels, and recovery of serum sodium and

urine osmolality after the administration of desmopressin [1-3]. In the present cases, hypernatremia, high plasma osmolality, low urine osmolality, and low plasma ADH levels (except case 1) with a good response to desmopressin (except case 3) easily led to the diagnosis of CDI. Spontaneous recovery from hypernatremia in case 3 might have been due to temporary dysfunction of the hypothalamic-neurohypophyseal axis, and the other two cases had permanent dysfunction. Water and electrolyte homeostasis in newborns is affected by postnatal adaptations, and appropriate management is important, especially for critical severe cases, such as those with asphyxia. The onset of CDI in the present cases was after one week of age. In severe asphyxia cases, follow-up of serum sodium and serum and urine osmolalities is necessary after the acute phase.

The MRI findings of the present cases, except case 1, showed normal posterior pituitary intensity, despite diffuse white matter damage and basal ganglia and thalamus damage. Typical neuroimaging findings of CDI, including absence of the posterior pituitary hyperintensity, are usually associated with germinoma, lymphocytic hypophysitis, or Langerhans cell histiocytosis [10]. Nevertheless, the identification of posterior pituitary hypointensity is nonspecific, and it does not necessarily indicate that the functional integrity of the hypothalamic-neurohypophyseal axis is preserved [9]. The normal endocrine function, except for central hypothyroidism in case 1, might be due to the greater sensitivity of the hypothalamic-neurohypophyseal axis to perinatal asphyxia than other endocrine functions.

In conclusion, three cases with CDI caused by severe asphyxia were described. Although such cases are rare, early diagnosis and treatment are indispensable to improve the prognosis of perinatal asphyxia. Follow-up of serum sodium levels and serum and urine osmolalities is necessary after the acute phase to maintain water and electrolyte homeostasis in cases of severe perinatal asphyxia.

Conflict of Interest

The authors declare no conflicts of interest.

Informed consents were obtained from the parents.

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