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Case report

Parieto-occipital encephalomalacia in neonatal hyperammonemia with ornithine transcarbamylase deficiency: A case report

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Abstract

Urea cycle disorders are congenital metabolic disorders that often cause episodic hyperammonemia. Neuroimaging in episodic hyperammonemia demonstrates several patterns of brain injuries, including focal lesions in the lentiform nucleus, insula, cingulate gyrus, and perirolandic fissure, as well as diffuse cerebral edema. In cases with neonatal onset of hyperammonemia, similar lesions have also been reported. We herein report a boy with severe neonatal hyperammonemia caused by ornithine transcarbamylase deficiency. He presented with parieto-occipital encephalomalacia, which resembles severe neonatal hypoglycemia on magnetic resonance imaging. This radiological finding may indicate parieto-occipital vulnerability not only to hypoglycemia but also to hyperammonemia.

Keywords: Neonate; Hyperammonemia; Urea cycle disorder; Ornithine transcarbamylase deficiency; Occipital lesion

1. Introduction

Urea cycle disorders (UCDs), including ornithine transcarbamylase deficiency (OTCD), carbamoyl phosphate synthetase I deficiency (CPSD), and hypercitrullinemia, are congenital metabolic disorders that often cause episodic hyperammonemia [1].

Transient hyperammonemia causes a brain insult that can be detected on neuroimaging. Neuroimaging in episodic hyperammonemia complicated with UCDs demonstrates diffuse brain edema in infants [2,3]. In episodes in children and adults, stroke-like lesions [4,5] or focal lesions of the lentiform nucleus, insula, cingulate gyrus, or perirolandic fissure [6,7] have been reported. In neonatal cases, similar focal cerebral lesions were also reported [8]. On the other hand, a diffuse, destructive, cerebral lesion appears in severe neonatal cases [9].

Neonatal parieto-occipital atrophy or encephalomalacia is a characteristic cerebral injury that appears with prolonged hypoglycemia [10]. The pathophysiology of this parieto-occipital lesion, which arises only in the neonatal period, has not been clarified, even though many researchers have tried. In neonatal hyperammonemia, one CPSD case resulting in similar parieto-occipital encephalomalacia has been reported [11].

Here, we report a boy with neonatal hyperammonemia caused by OTCD, who showed parieto-occipital encephalomalacia on neuroimaging.

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2. Case report

The present patient was the third son of non-consanguineous, healthy parents. In the family history, one maternal girl cousin was diagnosed as having OTCD when she developed hyperammonemia at age 10 months. The patient was born at 37 weeks gestation, with a birth weight of 2900 g (−0.25 SD), a body length of 48.0 cm (−0.48 SD), and a head circumference of 32.5 cm (−0.71 SD). The Apgar score was 10 at 5 min. The patient had no anomalies. The serum sugar was 102 mg/dl at birth. He did not appear aggravation of his vital signs or other symptoms which suggested hypoglycemia. Breast-feeding started from the day of birth. On day 2, his vitality and sucking deteriorated, and seizures began. Cranial computed tomography demonstrated no abnormal findings. The patient was admitted to the neonatal intensive care unit and required mechanical ventilation because of apnea. The blood pressure was 93/58 mm Hg. The serum ammonia was 952 μmol/L. Ultrasonography for the brain revealed slight narrow lateral ventricles and no abnormal intensities in the cerebrum. The resistant index of the anterior cerebral artery flow mildly decreased to 0.53 (normal range, 0.6–0.8). On day 3, the serum ammonia increased to 3542 μmol/L, and the serum glucose ranged from 76 to 277 mg/dl. Serum amino acid analyses showed: glutamate, 183.6 μmol/L (normal range, 12.6–62.5 μmol/L); glutamine, 6440.9 μmol/L (normal range, 422.1–703.8 μmol/L); citrulline, 0 μmol/L (normal range, 17.1–42.6 μmol/L); and ornithine, 1070.7 μmol/L (normal range, 31.3–104.7 μmol/L). Urinary orotate was 1744.9 μmol/L Cr (normal range, 8.4–25.8 μmol/L Cr). Hemodiafiltration, as well as administration of intravenous arginine and sodium benzoate, was started. From day 4, the serum ammonia level decreased and stabilized in the range of 160–197 μmol/L. The patient's respiration recovered. An electroencephalogram on day 5 demonstrated a flat pattern. On day 8, the patient started milk, but he required tube-feeding because of dysphagia. On day 9, additional administration of carnitine and lactulose was started. On day 15, the electroencephalogram showed recovery of cerebral activity except for the occipital lobes bilaterally. From day 15, the serum ammonia normalized. On day 89, microcephaly with a body weight of 4300 g (−1.7 SD), a body length of 50.0 cm (−3.6 SD), and a head circumference of 36.5 cm (−2.7 SD) were noted. The patient could not control his head, suck, or swallow. Deep tendon reflexes were exaggerated, and ankle clonus appeared bilaterally.

3. Neuroimaging

On day 12, the entire cerebral white matter showed edematous and diffuse low signal intensity on T1-weighted axial image (Fig. 1A) and diffuse high signal intensity on mid-sagittal T2-weighted image, corpus callosum showed very thick and pons showed high signal intensity (Fig. 1B). Diffusion-weighted imaging revealed high intensity lesions in the corpus callosum, internal capsule, optic radiation (Fig. 1C), and cerebral peduncle (not shown), as well as scattered lesions throughout the entire cerebral cortex predominantly in the posterior (Fig. 1C).

On day 89, T1-weighted MR images revealed global cerebral atrophy, slight high signal intensity in the cerebral white matter, and encephalomalacia in bilateral parieto-occipital lobes (Fig. 2A and B). No deformations or signal changes were obvious in the cerebellum and the brainstem (not shown).

4. Discussion

Parieto-occipital lesions following episodic hyperammonemia are very rare neuroradiological findings. To the best of our knowledge, only one case of episodic neonatal hyperammonemia in hypercitrullinemia with similar cerebral lesions has been previously reported [11]; hypersusceptibility specific to the neonatal period to some kind of amino acids in the parieto-occipital areas was presumed to be the cause of the characteristic lesions [11]. Episodic hyperammonemia in these disorders causes excessive consumption of alpha-ketoglutaric acid, which causes elevation of extracellular glutamate in the brain [7,12].

On the other hand, parieto-occipital lesions in neonates are well known in prolonged neonatal hypoglycemia. In severe cases of this pathophysiology, the lesions develop to polycystic encephalomalacia in the parieto-occipital lobes, which is similar to the lesions observed in the present case [10]. Neonatal hypoglycemia also increases glutamate in brain tissue [13].

Neonatal occipital regions show age-dependent vulnerability to excitotoxicity that is mediated by *N*-methyl-D-aspartate-type glutamate receptors [14]. Elevated glutamate might be a cause of the parieto-occipital lesions that appear in the two types of UCDs, OTCD and hypercitrullinemia, and neonatal hypoglycemia.

Meanwhile, posterior lesions also appear in a part of hypoxic–ischemic encephalopathy in asphyxia of term infant [15]. However, obvious reduced cerebral blood circulation or severe hypoxia was not suspected from his clinical or ultrasonographic findings.

Compared to the present case, milder cerebral lesions [8] and more destructive lesions [9] were observed in the previous reports of neonatal hyperammonemia. However, it is difficult to clarify the relationship between the severity of the neuroimaging findings and the degree of hyperammonemia in these previous cases, because the details of the serum ammonia course were not described. As in the present case, extreme hyperammonemia for