

A highly unusual case of osmotic demyelination syndrome and extrapontine myelinolysis in a 3-month-old infant with Bartter syndrome

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Abstract

Bartter syndrome (BS) is a rare autosomal recessive renal tubular disorder characterized by acute electrolyte imbalance, and similarly, osmotic demyelination syndrome (ODS) is a rather rare complication occurring during electrolyte imbalance. The pathological features of ODS include central pontine myelinolysis and extrapontine myelinolysis (EPM), which consist of severe damage to the myelin sheath of neurons. ODS is very rare in children. We describe a case of a 3-month-old infant with ODS and EPM associated with undiagnosed BS. ODS developed because of a sudden change in electrolyte levels and osmolality caused by acute dehydration during a gastrointestinal infection episode. Undiagnosed, untreated, and non-balanced BS was the cause of the neurological complication. Our patient represents the first case of ODS in BS, the ninth case of ODS in an infant less than one year old, and the third case of isolated EPM in such a young patient. This case report reminds us that in rare diseases, young patients tend to have genetic components.

Keywords

Osmotic demyelination syndrome, extrapontine myelinolysis, seizure, newborn, Bartter syndrome, electrolyte imbalance

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Introduction

Osmotic demyelination syndrome (ODS) is an uncommon complication of osmotic stress characterized by severe damage to the myelin sheath of pontine neurons (central pontine myelinolysis, CPM) and extrapontine sites (extrapontine myelinolysis, EPM). It was first described in 1959 by Adams *et al.* in alcoholic and malnourished patients.¹

ODS is diagnosed in patients undergoing pronounced alterations in plasma osmolality and is generally, but not always, linked to rapid correction of chronic hyponatremia. However, it can be associated with many other disorders or an electrolyte imbalance in which sodium levels may be normal or even high.²⁻⁴ In a large review, Singh *et al.*⁵ showed that the most common predisposing factor of CPM and EPM was hyponatremia (78%), and the most common presentation was encephalopathy (39%). Recognized predisposing factors include alcoholism, liver transplantation, malnutrition, and chronic debilitation states. ODS is rather rare in children, especially if isolated EPM cases are considered. In a recent review, Ranger *et al.*⁶ reported 76 pediatric cases, and only four were younger than 1 year. Two of these patients had CPM; one patient had both CPM and EPM, and the other patient presented with isolated EPM.

Bartter syndrome (BS) represents a set of closely related autosomal recessive renal tubular disorders characterized by hypokalemia, hypochloremia, metabolic alkalosis, and hyperreninemia with normal blood pressure. BS results from mutations in numerous genes that affect the function of ion channels and transporters that normally mediate transepithelial salt reabsorption in the thick ascending limb of the kidney. These abnormalities result in hypochloremia and hyponatremia with subsequent volume depletion; chronic hypovolemia

activates the renin–angiotensin–aldosterone system, with subsequent sodium reabsorption and potassium depletion. Clinical manifestations of BS can vary according to the genes involved and range from antenatal presentation with polyhydramnios to later onset with significant polyuria, failure to thrive, and dehydration.⁷ This case report reminds us that, in rare diseases, young patients tend to have genetic components, and moreover, multiple diseases are often associated.

Case report

Our patient was a female infant, second-born to consanguineous Pakistani parents. She was born at term in another hospital by spontaneous vaginal delivery. Her birth weight was 2900 g (32nd percentile). She had a normal extrauterine adaptation (Apgar score of 9 and 10 at the first and fifth minute, respectively), and she was discharged from the post-natal ward on day 3 of life, without other clinical follow-up.

At 3 months of age, she was brought to the pediatric emergency department (ED) with generalized seizures, characterized by tonic flexion of the upper limbs, tonic extension of the lower limbs, and right eye deviation. The first seizure terminated spontaneously in fewer than 7 minutes; the second seizure lasted for 20 minutes and stopped after intravenous lorazepam and phenobarbital administration. The parents reported similar events in the previous days.

The physical examination showed severe dehydration. Upon neurological examination, the patient was unresponsive and presented marked numbness, hypotonia, and hyporeactivity. Furthermore, she appeared malnourished with a weight of 3254 g (below the 3rd percentile). Laboratory investigations showed metabolic alkalosis (pH 7.56, PaCO₂: 47 mmHg, base excess: 18.2) and severe electrolyte impairment

with hyponatremia (122 mEq/L), hypokalemia (2.1 mEq/L), and hypochloremia (70 mEq/L). In the acute phase, magnetic resonance imaging (MRI) (Figure 1a, b, c) revealed a marked T2 signal abnormality involving the white matter of both centra semiovale with a strikingly symmetric distribution. This signal abnormality extended caudally converging toward the posterior limb of the internal capsules. In the

same location, diffusion appeared markedly restricted.

In the first hour after admission to the ED, the patient received an intravenous bolus of 60 mL of 0.9% sodium chloride because of the severe dehydration, and following adequate intravascular volume expansion, rehydration was achieved with appropriate fluids. Sodium chloride and potassium chloride were supplemented on

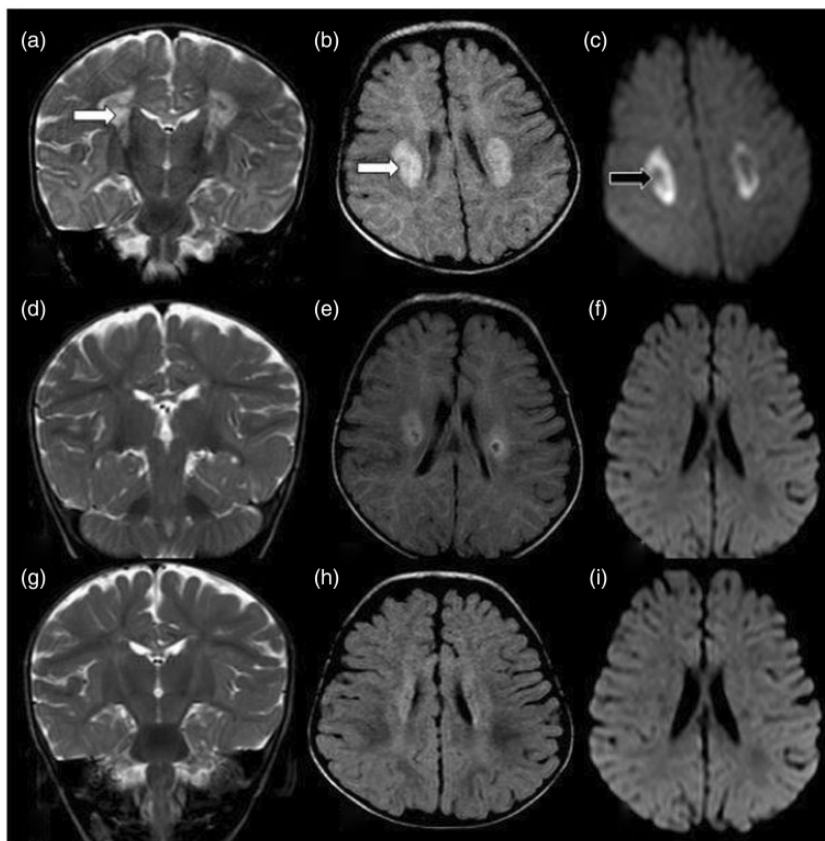


Figure 1. Magnetic resonance images obtained on day 1 after admission (first line, images a, b, and c), on day 14 after admission (second line, images d, e, and f), and 5 months later (third line, images g, h, and i). Coronal T2 fast spin-echo sections are shown in images a, d, and g; fluid-attenuated inversion recovery axial sections through the corona radiata and the upper portion of the lateral ventricles are shown on images b, e, and h; axial diffusion-weighted imaging sections through the corona radiata are shown in images c, f, and i. Prominent T2 hyperintensities (white arrows) in the white matter of both hemispheres are symmetric, apparently depicting the pyramidal tracts, and extended caudally towards the internal capsules. Diffusion is markedly restricted in the same location (black arrow). On follow-up studies, the lesions progressively regressed and almost completely vanished at 5 months.

the basis of electrolyte blood levels, which were strictly checked to avoid an extremely rapid correction of the electrolyte impairment.

During the following weeks, the patient required supplementation of potassium and sodium chloride to achieve electrolyte serum level normalization and clinical improvement.

On admission, an accurate medical history revealed diarrhea in the days preceding the event, and the parents disclosed that the patient was fed with diluted formula milk. In addition, the family history revealed that a sister of the patient was affected by type III BS.

At that time, based on the clinical suspicion of BS, indomethacin was started. BS was later confirmed by genetic investigations, which showed a homozygous nucleotide substitution, c.910C>T, in exon 9 of the *CLCNKB* gene (a chloride channel gene located on chromosome site 1p36) that was consistent with type III BS. The sister carried the same homozygous mutation, and the parents were both heterozygous for the mutation.

After 2 weeks, follow-up MRI showed partial resolution of brain lesions, which appeared more limited on T2 sequences, and almost complete normalization of the diffusion test (Figure 1d, e, f). Finally, at 5 months, MRI revealed regression of the cerebral lesions, which had almost completely resolved (Figure 1g, h, i).

Currently the patient is 1 year old. Her last neurologic examination revealed good eye contact and mild axial hypotonia. No cerebellar or pyramidal tract signs were noticed. Primitive reflexes and tendon reflexes were diminished but normally evoked. Her visual and hearing function assessments were normal.

Discussion

ODS is a neurological complication with a prevalence of 0.25% to 0.5% in the general

population, and its occurrence in infancy is extremely rare.⁸ It is caused by severe and prolonged hyponatremia, particularly when corrected too rapidly. It has also been described in association with hypernatremia and serum hyperosmolality.¹ Hypokalemia is another risk factor for ODS.^{9,10}

The pathogenesis of ODS is complex and involves the inability of brain cells to respond to rapid changes in interstitial compartment osmolality, leading to dehydration of energy-depleted cells and alteration of the blood–brain barrier.^{11,12}

In the setting of rapid correction of hyponatremia, brain cells attempt to increase the intracellular inorganic ion content and the production of organic osmolytes.¹¹ However, this process represents a significant metabolic strain on glial cells, leading to ATP depletion, during which healthy cells accumulate glucose provisions, presumably in anticipation of inevitable future demands.¹³ Therefore, although hyponatremia is one of the most frequent electrolyte imbalances in medicine, its correction rarely leads to ODS. In patients with liver failure, alcoholism, or malnutrition, glial cells are particularly vulnerable to energy deprivation, leading to failure to respond to changes in extracellular osmolality and to regulate their cellular volume. The resultant shrinkage of glial cells may lead to axonal damage and disruption of tight junctions.^{11,12,14}

ODS lesions are typically symmetrical and sharply demarcated, and during the active phase of the disease, they contain sheets of lipid-laden macrophages and a large number of reactive astrocytes. In contrast to other demyelinating diseases, an inflammatory component is absent, and if multiple foci of demyelination are present, they all exhibit the same stage of demyelinating activity. The areas most frequently involved other than the pons are the cerebellum, lateral geniculate bodies, external

and extreme capsules and subcortical white matter, basal ganglia, and thalami.¹⁵

Myelinolysis was once thought to be rare, but a study in an unselected urban hospital population group showed an incidence of 3/1000¹⁶ with CPM much more frequent than EPM.

The clinical presentation of CPM differs from that of EPM. In CPM, patients show a biphasic clinical course, initially presenting with seizures caused by hyponatremia, then recovering as soon as normonatremia is restored, only to deteriorate several days later with symptoms secondary to corticobulbar fiber involvement (dysarthria and dysphagia) or corticospinal tract involvement (flaccid quadriplegia). An illusory change in the consciousness level may occur, reflecting "locked-in syndrome". Movement disorders (dystonia, parkinsonism, catatonia) occur in some patients and are likely related to EPM.^{1,17}

MRI is the imaging technique of choice for ODS; it reveals pontine and extrapontine hyperintensities on T2 and hypointensities on T1-weighted images without contrast enhancement. Diffusion weighted imaging exhibits diffusional restriction and might have the capability to detect lesions undetectable on T2 images.¹⁸⁻²⁰ Multifocal EPM features on MRI may also be observed in some disorders such as ischemia, multiple sclerosis, tumors, and metabolic disease, but they are diagnostic of ODS when symmetrical. During the subacute and chronic phases, lesions become smaller and better defined, and they may resolve completely.²¹

We presented a case of EPM in a patient with undiagnosed BS during a gastrointestinal infection and a history of feeding with diluted formula milk. ODS was not linked to a rapid correction of serum electrolytes because it was already evident on MRI performed on admission in the ED. In our opinion, dehydration caused by infection, malnutrition, and feeding with low-sodium

concentration formula worsened the patient's borderline hydro-electrolyte balance resulting from the unrecognized BS, triggering ODS symptoms.

Furthermore, the diagnosis is supported by the MRI follow-up results; on the day of admission, a marked T2 alteration involving the white matter of both centra semiovale, which extended caudally and converged toward the posterior limb of the internal capsules, was visible, with a strikingly symmetric distribution. In the same location, diffusion was markedly restricted. The impressive restriction in water mobility causing restricted diffusion was strongly suggestive of a state of cytotoxic edema caused by impaired control of membrane electrolyte movement. Because the distribution was bilateral, symmetric, and confined to a specific anatomic pathway, namely the motor tract, the possibility of an ischemic etiology was excluded. Two weeks later, after correction of the electrolyte impairment and during progressive clinical recovery, MRI showed a partial regression in the lesion pattern, and the T2 hyperintensities were more limited, with almost complete diffusion normalization (Figure 1d, e, f). Five months later, complete resolution was demonstrated on MRI (Figure 1g, h, i).

Another peculiarity of our case is the location of the lesions. Univocal interpretations to justify the involvement of the white matter of both centra semiovale and the posterior limb of the internal capsules are not available; however, a hypothesis was proposed. In the first months of life, white matter represents the brain areas with greater energy expense because it consists of glial elements in active proliferation and differentiation, and it is the site of intense metabolic activity because of the synthesis of myelin by oligodendrocytes. For these reasons, it is also one of the most vulnerable areas in the brain. Therefore, blood provision might not be

sufficient to support the increased energy demand in some conditions, such as exacerbation by osmotic stress, hence resulting in myelinolysis. In our patient, the precarious balance caused by BS could have caused this area to be more liable to pathogenic insults.

There are few pediatric cases of ODS with EPM in the literature; in the latest review by Bansal and Zinkus, 106 cases of ODS were analyzed from 1960 to 2018. Eighty-three of 106 cases were pediatric patients; 41% presented CPM alone, and 29% had both CPM and EPM. While isolated EPM was identified in 30% of patients, only eight were younger than 1 year of age (9.6%).²² These eight patients ranged from 1 to 11 months of age, and only three children presented EPM (two 9-month-old patients and one 11-month-old patient); two patients had CPM (6 and 10 months old), and the last three children presented both CPM and EPM (a 1-month-old child and two 11-month-old children). Regarding the outcome of pediatric ODS, a full recovery is expected in 20% of patients; in almost 23%, a mild-to-moderate neurological deficit may persist, and more than 50% may die within days or weeks of the onset of neurological manifestations.⁶ In the eight infants younger than 1 year of age, four had a complete recovery, two had a partial recovery, and one died (recovery data for this child are not available). To our knowledge, our patient represents the first case of ODS in BS, the ninth case of ODS in an infant less than 1 year old, and the third case of isolated EPM in such a young patient. This rare occurrence is likely caused by the ongoing process of myelination, which takes place before 2 years of age. Supratentorial white matter myelination occurs later than pontine myelination; therefore, EPM is even rarer.²³

In conclusion, we hypothesize that the infant developed ODS because of a

sudden change in electrolyte levels and osmolality because of acute dehydration during a gastrointestinal infection episode. Her background of undiagnosed (and therefore untreated and uncontrolled) BS was the basis for her precarious electrolyte balance. A diagnosis of ODS was established on the basis of clinical, laboratory, and imaging data. The symmetric distribution of the lesions on MRI, the strong diffusion restriction, and the circumscribed localization to the white matter of both centra semiovale converging toward the posterior limb of the internal capsule on acute MRI are considered the classical spectrum of this condition, together with the full healing of the lesions after a few months and the nearly clinical recovery after gradual normalization of the hydro-electrolyte disorders. In our case, the slow correction of electrolyte imbalance allowed us to control ODS and to prevent deterioration as indicated by both clinical and neuroimaging improvement.

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Ethics statement

Written consent was obtained from the patient's parents for publication of this case report in accordance with the principles of the Declaration of Helsinki

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Author contributions

GG and DF conceived the manuscript and critically revised the final proof. CS and SP wrote the first draft of the manuscript. FDD and MM revised the recent literature. All authors approved the final version.

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References

- Martin RJ. Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes. *J Neurol Neurosurg Psychiatry* 2004; 75: iii22–iii28.
- Aoki R, Morimoto T, Takahashi Y, et al. Extrapontine myelinolysis associated with severe hypernatremia in infancy. *Pediatr Int* 2016; 58: 936–939.
- Kinoshita H, Grant L, Xoinis K, et al. Central pontine myelinolysis in pediatric diabetic ketoacidosis. *Case Rep Crit Care* 2018; 2018: 4273971.
- King JD and Rosner MH. Osmotic demyelination syndrome. *Am J Med Sci* 2010; 339: 561–567.
- Singh TD, Fugate JE and Rabinstein AA. Central pontine and extrapontine myelinolysis: a systematic review. *Eur J Neurol* 2014; 21: 1443–1450.
- Ranger AM, Chaudhary N, Avery M, et al. Central pontine and extrapontine myelinolysis in children: a review of 76 patients. *J Child Neurol* 2012; 27: 1027–1037.
- Deschênes G and Fila M. Primary molecular disorders and secondary biological adaptations in Bartter syndrome. *Int J Nephrol* 2011; 2011: 396209.
- Bansal LR. Therapeutic effect of steroids in osmotic demyelination of infancy. *Child Neurology Open* 2018; 5: 1–4. doi: 10.1177/2329048X18770576.
- Lohr JW. Osmotic demyelination syndrome following correction of hyponatremia: association with hypokalemia. *Am J Med* 1994; 96: 408–413.
- Love S. Demyelinating diseases. *J Clin Pathol* 2006; 59: 1151–1159.
- Ashrafian H and Davey P. A review of the causes of central pontine myelinolysis: yet another apoptotic illness? *Eur J Neurol* 2001; 8: 103–109.
- Murase T, Sugimura Y, Takefuji S, et al. Mechanisms and therapy of osmotic demyelination. *Am J Med* 2006; 119: S69–S73.
- Fillenz M, Lowry JP, Boutelle MG, et al. The role of astrocytes and noradrenaline in neuronal glucose metabolism. *Acta Physiol Scand* 2000; 167: 275–228.
- Adler S, Verbalis JC and Williams D. Effect of rapid correction of hyponatremia on blood–brain barrier of rats. *Brain Res* 1995; 679: 135–143.
- Nicaise C, Marneffe C, Bouchat J, et al. Osmotic demyelination: from an oligodendrocyte to an astrocyte perspective. *Int J Mol Sci* 2019; 20: 1124.
- Huq S, Wong M, Chan H, et al. Osmotic demyelination syndromes: central and extrapontine myelinolysis. *J Clin Neurosci* 2007; 14: 684–688.
- Hurley RA, Filley CM and Taber KH. Central pontine myelinolysis: a metabolic disorder of myelin. *J Neuropsychiatry Clin Neurosci* 2011; 23: 369–374.
- Chua GC, Sitoh YY and Lim CC. MRI findings in osmotic myelinolysis. *Clin Radiol* 2002; 57: 800–806.
- Alleman AM. Osmotic demyelination syndrome: central pontine myelinolysis and extrapontine myelinolysis. *Semin Ultrasound CT MR* 2014; 35: 153–159.
- Orgel A, Hauser TK, Nagele T, et al. Image findings in central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM). *Rofo* 2017; 189: 103–107.
- Miller MG, Baker HL, Okazaki H, et al. Central pontine myelinolysis and its imitators: MR findings. *Radiology* 1988; 168: 795–802.
- Bansal LR and Zinkus T. Osmotic demyelination syndrome in children. *Pediatr Neurol* 2019; 97: 12.
- Tarhan NC, Firat A, Otken A, et al. Central pontine myelinolysis secondary to cytomegalovirus hepatitis in a 10 month-old child. *Pediatr Radiol* 2003; 33: 44–46.