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RECURRENT HYPONATREMIA IN A 16 YEAR OLD FEMALE WITH ACUTE INTERMITTENT PORPHYRIA

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ABSTRACT

Hyponatremia is one of the most frequent laboratory findings in hospitalized children. We present an unusual case of recurrent hyponatremia in a 16-year-old female secondary to acute intermittent porphyria (AIP), a rare inborn error of metabolism. The proposed mechanism of the hyponatremia and recommended treatment are discussed. Although rare, AIP should be considered in children with recurrent hyponatremia who present with signs and/or symptoms characteristic of the disease.

INTRODUCTION

Hyponatremia is one of the most frequent laboratory findings in hospitalized children. One or more episodes of hyponatremia have been reported in approximately 20% of patients hospitalized for more than a day.[1] Hyponatremia is associated with significant morbidity, including seizures, and can be fatal. In general, hyponatremia tends to be self-limiting and treatment is based upon the underlying etiology. We present a 16-year-old female who presented with recurrent hyponatremia, abdominal pain and hypertension, who was found to have acute intermittent porphyria.

CASE PRESENTATION

A 16-year-old autistic female with a history of epilepsy presented to the Emergency Department complaining of severe abdominal pain. At the time of presentation, her serum sodium was 124 mEq/L (reference range: 135-145 mEq/L) and she was hypertensive (138/94 mmHg). Her hypertension was thought to be secondary to post-streptococcal glomerulonephritis and the hyponatremia attributed to carbamazepine. Shortly after hospital admission, she experienced a generalized tonic-clonic seizure and was transferred to the PICU for treatment and monitoring. Her pain spontaneously resolved, following which her blood pressure and hyponatremia improved. Her blood pressure and pain medications were discontinued and she was discharged.

Three months later, she again presented to the Emergency Department with abdominal pain and hypertension, receiving medications for both. She was found to have a fecal impaction. Following an enema, her blood pressure and pain improved. Pain and blood pressure medications were discontinued and she was discharged.

Her third hospital admission was preceded by several days of abdominal pain and bilious emesis. On the day of admission, her sodium was 141 mEq/L with a blood pressure of 140/100 mmHg. The hypertension was attributed to her pain, and she was treated with hydralazine, which was later changed to amlodipine. Imaging studies demonstrated a superior mesenteric artery syndrome, with compression of the distal third of the duodenum between the aorta and superior mesenteric artery. A nasojejunal tube was placed for feeding.

During hospitalization, her sodium progressively declined to 126 mEq/L (**Figure 1**). Although the serum sodium improved transiently following administration of intravenous hypertonic saline, hypertension and pain persisted. In addition to intermittent, severe abdominal pain, hyponatremia, and hypertension, she was noted to have dark colored urine, prompting measurement of urinary porphobilinogen. After receiving intravenous saline with 10% dextrose, her abdominal pain, hypertension, and hyponatremia rapidly resolved.

Results of her diagnostic testing confirmed the clinical suspicion of porphyria (**Table 1**). Genetic testing revealed a previously reported deletion of the HMBS allele (c.1084delT). Zonegran, an anti-epileptic medication

Figure 1. Changes is Serum Sodium

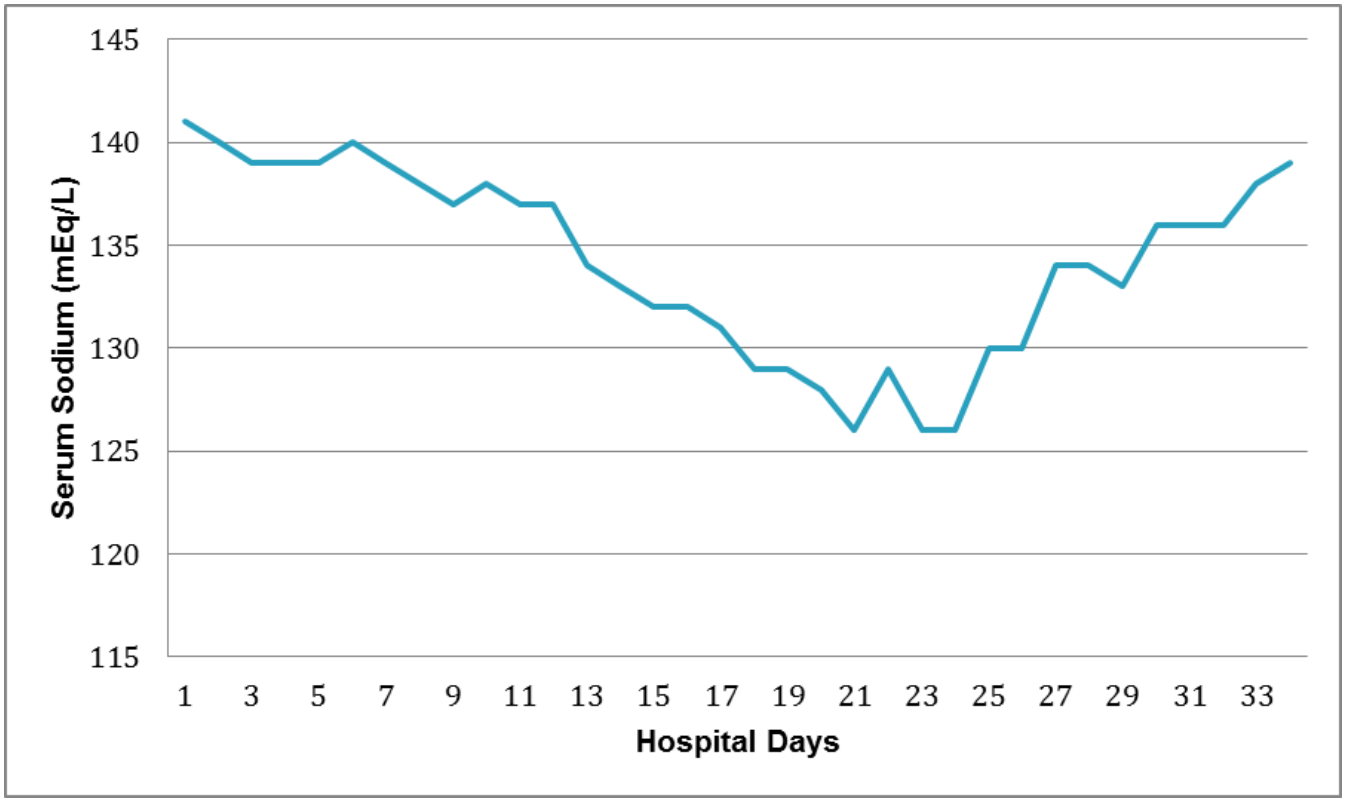

Table 1. Diagnostic Test Results

Test	**Results**	**Reference Range**
Porphyrins, urine	140.1	0.0 – 8.8 µmol/L
Porphyrins, fecal		
Coproporhyrin, Feces	28	0 – 45 nmol/g
Protoporphyrin, Feces	17	0 – 100 nmol/g
Porphyrin Fecal Interpretation	Negative	
Genetic Testing	**Gene Analyzed**	**Results**
Acute Intermittent Porphyria	HMBS	c.1084delT
Hereditary Coproporphyria	CPOX	No mutation detected
Variegate Porphyria	PPOX	No mutation detected

thought to be porphyrinogenic, was discontinued, as well as all anti-hypertensive medications, and she was discharged with a nasojejunal tube for enteral feedings until oral intake improved.

DISCUSSION

Hyponatremia (serum sodium < 135 mEq/L) is a common electrolyte abnormality found in approximately one out of every five hospitalized patients.[1] Skillful management is required since a 60-fold increase in mortality has been reported in individuals with hyponatremia.[2] Treatment of hyponatremia is aimed at addressing the underlying cause, if possible, as well as the duration and severity of the hyponatremia, and upon the presence and severity of symptoms. Hypovolemic hyponatremia is best corrected by isotonic saline, while the general approach to euvolemic and hypervolemic hyponatremia consists of fluid restriction. Lithium carbonate, demeclocycline, urea and loop diuretics may be considered if prolonged treatment is needed, but may have undesirable side effects, especially in growing children. Finally, although experience is limited in children and use in adults has been associated with serous limitations, vasopressin receptor antagonists have been become available.

Common signs and symptoms of hyponatremia include hypotension, fatigue, headache, seizure, muscle weakness, and in extreme cases, altered mental status and coma. A review of the history and results of laboratory tests is helpful in determining the etiology of hyponatremia, commonly due to gastroenteritis, hypotonic fluid replacement, use of diuretics, and hypothyroidism. Once common etiologies have been excluded, other rare conditions should be considered.

In the case presented, the hyponatremia was secondary to acute intermittent porphyria (AIP). AIP is a rare autosomal dominant inborn error of metabolism of the heme synthesis pathway. It occurs in approximately 1.5:100,000 and is more common in females 18 to 40 years of age.[3] AIP is due to a mutation or deficiency in the enzyme porphobilinogen deaminase (PBGD), leading to an accumulation of the intermediate metabolites, delta-aminolevulinic acid and porphobilinogen. Patients with AIP present with episodes of intermittent, spastic abdominal pain often accompanied by vomiting and seizures. Peripheral neuropathy and psychiatric symptoms that mimic several other disorders may occur. In contrast to other forms of porphyria, AIP lacks cutaneous manifestations.

Laboratory findings include elevated levels of urinary ALA and PBG. Two rapid screening tests for AIP include discoloration of the urine to a deep red or purple upon exposure to sunlight (when exposed to light, the colorless porphyrinogens undergo conversion to purple colored porphyrinogens) and the Hoesch Test (urine that contains porphobilinogens turn a red color with the addition of hydrochloric acid).[4]

There is no cure for AIP. Treatment includes management of acute attacks with glucose loading and avoidance of medications, heavy metals and conditions that are known to be porphyrinogenic, such as alcohol consumption, and starvation.

In addition to intermittent pain crises, hyponatremia is one of the most common manifestations of AIP.[5] Hyponatremia may contribute to the morbidity and mortality in affected individuals. Although the etiology of the hyponatremia is incompletely understood, it is believed to be the result of syndrome of inappropriate antidiuretic hormone (SIADH).[6] Acute attacks of AIP are thought to damage the hypothalamic-hypophyseal tract and cause vacuolization of neurons in the supraoptic nucleus, leading to a leakage of ADH into the circulation.[4] Vomiting and lack of food intake during acute attacks can also contribute to hyponatremia. The euvolemic, hyponatremia caused by SIADH can be managed with fluid restriction. Vasopressin receptor antagonists, acting through V2-receptors located on the principal cells of the renal collecting tubule[7], are available but associated with serous limitations. Glucose appears to be effective in improving symptoms by inhibiting δ-aminolevulinic acid synthase activity and protoporphyrin synthesis.

Medications that induce the formation of the cytochrome P450 family of liver enzymes can aggravate porphyria. Heme, the final product of the porphyrinogen pathway, is used to make enzymes utilized by cytochrome P450; thus, any increase in the production of the P450 family will increase production of heme, which can trigger an attack.[4] The hypoglycemia that occurs in starvation can lead to disinhibition of δ-aminolevulinic acid synthase by glucose, exacerbating AIP. In addition, alcohol has been found to induce δ-aminolevulinic acid synthase and inhibit several of the downstream enzymes involved in

the heme synthesis pathway, thus leading to an accumulation of porphyrinogens and worsening of AIP.[8]

CONCLUSION

Acute intermittent porphyria is a rare cause of unexplained hyponatremia. Although the etiology of the hyponatremia in individuals with AIP is incompletely understood, it is believed to be the result of inappropriate secretion of anti-diuretic hormone. Treatment is generally supportive and consists of intravenous glucose and avoidance/discontinuation of porphyrinogenic medications, alcohol, and starvation. Diagnosis of AIP requires a high index of suspicion. Although rare, acute intermittent porphyria should be considered in children with recurrent hyponatremia and clinical manifestations characteristic of the disease.

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