CASE REPORT

Acute Intermittent Porphyria: A rare cause of hyponatraemia

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Abstract

Introduction: Hyponatraemia is one of the most frequent laboratory findings in hospitalised patients. We present an unusual case of hyponatraemia in a 23-year-old female secondary to acute intermittent porphyria (AIP), a rare inborn error of metabolism. Case Report: The patient presented with upper respiratory tract infection, fever, seizures and abdominal pain. An initial diagnosis of encephalitis was made. In view of the unexplained abdominal pain with other clinical findings such as posterior reversible encephalopathy syndrome by CT brain, temporary blindness as well as hyponatraemia, acute intermittent porphyria was suspected. Urine delta aminolaevulinic acid (δ-ALA) and porphobilinogen were elevated confirming the diagnosis of AIP. Genetic studies were done for this patient. The patient had a complete resolution of her symptoms with carbohydrate loading and high caloric diet. Conclusion: Although rare, AIP should be considered as a cause of hyponatraemia in a patient who presents with signs and/or symptoms that are characteristic of this disease.

Keywords: Acute intermittent porphyria; porphyria; hyponatraemia; syndrome of inappropriate secretion of anti-diuretic hormone (SIADH).

INTRODUCTION

Hyponatraemia is an important electrolyte disorder frequently encountered in clinical practice.¹ Hyponatraemia is defined as plasma sodium level below 135 mmol/L. The prevalence of hyponatraemia has been observed to be as high as 30% in hospitalised patients.² It is associated with significant morbidity, including neurological sequelae, and if severe enough can be fatal. In general, hyponatraemia tends to be a self-limiting and treatment varies depending on the underlying aetiology. We report a 23-year-old female who presented with severe hyponatraemia, abdominal pain, hypertension and posterior reversible encephalopathy syndrome (PRES), who was diagnosed with acute intermittent porphyria (AIP).

CASE REPORT

A 23-year-old Chinese lady with no past medical history presented with 4 days history of fever, sore throat, abdominal pain and vomiting. She was treated as pharyngitis and given a course of antibiotics. However, her symptoms did not improve, and was hospitalised elsewhere. Her serum sodium was noted to be low and she developed tonic clonic seizures. One week later, she developed sudden bilateral painless vision loss. In view of the clinical profile, the diagnosis of encephalitis was made. CSF analysis did not show any abnormality. She was noted to have high blood pressure at that time. She commenced on sodium valproate for her convulsions and telmisartan/amlodipine for hypertension. She was referred to our hospital for further evaluation and management. She had been previously healthy with no past family history of neurological deficit.

At the time of admission, she was afebrile with a temperature of 36.9°C, blood pressure of 133/78 mmHg and heart rate of 114 beats per minute. Cardiovascular examination revealed tachycardia and respiratory examination was normal. Her abdomen was soft, there was no organomegaly. Physical examination of the central nervous system showed no abnormality except for reduced sensation in a glove distribution.

The ECG showed sinus tachycardia and the chest X-ray was normal. The computed tomographic (CT) of the brain showed symmetrical white matter hypodensities seen at
frontal, parietal and occipital lobes suggestive of posterior reversible encephalopathy (Fig. 1). The provisional diagnosis at that time was PRES in view of the clinico-radiological findings. To rule out the unexplained neurological symptoms, autoimmune screening was done and the results were normal.

Laboratory data at admission in our hospital revealed a serum sodium level of 111 mmol/L. Urine sodium and osmolality were 204 mmol/L and 459 mOsm/kg respectively. Serum osmolality was noted to be only 237 mOsm/kg. A work-up for hyponatraemia including serum cortisol and thyroid function test were done for this patient. The results were normal which excludes adrenal insufficiency and hypothyroidism as the cause of hyponatraemia. In view of low serum osmolality in the euvolemic state with high urine sodium and osmolality the diagnosis of SIADH was considered.

Her serial biochemical blood results are shown in Table 1. The sodium level remained low in spite of treatment and her blood pressure was persistently elevated requiring additional anti-hypertensive medications.

In addition, the patient had persistent abdominal pain and at times, the pain was severe enough that required regular multiple doses of tramadol. An abdominal-pelvic CT with intravenous contrast was done for this patient and features suggestive of sigmoid colitis were noted. However, sigmoidoscopy did not reveal any abnormality.

In view of persistent hyponatraemia, abdominal pain, hypertension and neurological symptoms with characteristic CT scan findings; AIP was suspected. Urine porphobilinogen (PBG) was noted to be positive. Urine delta-aminolevulinic acid (δ-ALA) was measured and the level was 21.56 (normal value <2.6 mmol/mol creatinine). Urine and stool porphyrin were not done for this patient. Laboratory results confirmed the clinical suspicion of porphyria. Genetic testing showed a heterozygous mutation in exon 10 (c.503G>T p. (Gly168Val)) that encoded hydroxymethylbilane synthase enzyme.

She was started on a high carbohydrate diet and the sodium valproate as well as the anti-hypertensive medication were stopped. Her vision has also improved significantly. One week later, she recovered completely and discharged. The family was counselled regarding the disease and the potential factors that could trigger an acute episode but no genetic testing was performed for the family members.

**DISCUSSION**

Hyponatraemia is the most common electrolyte disorder and is associated with a variety of underlying diseases and conditions. Hyponatraemia has been associated with a 60-fold increase in morbidity and mortality compared with patients without documented hyponatraemia. The management of hyponatraemia depends on the aetiology of this condition. The aetiology of most cases of hyponatraemia can be deduced from the history, physical examination and basic laboratory tests. Once common aetiologies have been excluded, other rare conditions should be considered.

Our patient presented with severe hyponatraemia which was due to AIP. AIP is a rare metabolic disease due to deficiency of HMBS (also known as porphobilinogen deaminase) that leads to the accumulation of porphyrin precursors; porphobilinogen (PBG) and aminolaevulinic acid (ALA). Hydroxymethylbilane synthase (HMBS), which is the third enzyme in the haem biosynthesis pathway catalyses the polymerisation of PBG.

**FIG. 1:** Plain CT of the brain showing symmetrical white matter hypodensities seen at frontal (A), parietal (B) and occipital (C) lobes.
to hydroxymethylbilane. AIP is estimated to affect about one in 75000 people in European countries. In Malaysia AIP is a very rare disorder. AIP is an autosomal dominant disorder displaying incomplete penetrance; thus the likelihood of an individual with HMBS mutation having an acute attack is small. This could be the probable reason that our patient did not have a positive family history. However, the family members were not screened for the disorder.

Acute attacks usually occur after puberty and more common in young females. Most patients present with severe abdominal pain, nausea, vomiting, constipation and seizures. Peripheral neuropathy and psychiatric symptoms that may mimic several other disorders have been reported. They can also have symptoms of increased sympathetic activity such as sweating, tachycardia and hypertension. Hyponatraemia is found in approximately 20% of cases with symptomatic AIP as a result of inappropriately anti-diuretic hormone secretion. Hypothalamic damage and neuronal loss has been described as the cause of increased ADH. This explains hyponatraemia in this patient.

Sudden bilateral reversible vision loss is a rare neurological manifestation of AIP. Accumulation of haem precursors has been postulated to be the cause of direct neurotoxicity and results in neuronal dysfunction. Vasospasm also has been attributed to be a cause due to decreased biosynthesis of haem, with subsequent reduction of nitric oxide, which is a major vasodilator. Vasospasm in porphyria tends to be predominant in the posterior circulation. This accounts for the transient loss of vision and posterior reversible encephalopathy syndrome in our patient.

An acute attack is usually triggered by reduced calorie intake, medications (barbiturates, calcium channel blockers, antibiotics, and hormones), large alcohol intake, nicotine abuse, infection, surgery and psychiatric illness. Infections have been shown to precipitate acute attacks in 30% of cases. Inflammation and infection enhance the haem catabolism by upregulating the hepatic expression of acute-phase protein haem oxygenase 1. This leads to increased demand for hepatic haem synthesis and induces ALAS.

The varied spectrum of signs and symptoms of acute intermittent porphyria lead to diagnostic difficulty and porphyria is usually considered as a possible diagnosis after excluding other causes. The diagnosis of AIP in this patient was delayed due to the non-specific clinical manifestation. Hence, a high index of clinical suspicion is required for the diagnosis of AIP.

Once the physician suspects acute porphyria, the next step is to measure the urine PBG and ALA. In patients with an acute attack, the PBG level will typically be elevated whereas a normal PBG excludes an acute porphyria attack. The PBG level usually remains elevated for weeks in AIP. Treatment should be started immediately and any precipitating factors especially drugs

### Table 1: Serial monitoring of biochemical parameters

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Reference Interval</th>
<th>27/9</th>
<th>30/9</th>
<th>2/10</th>
<th>4/10</th>
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</thead>
<tbody>
<tr>
<td><strong>Serum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>135-145</td>
<td>111</td>
<td>119</td>
<td>122</td>
<td>129</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.5-5.0</td>
<td>3.5</td>
<td>3.9</td>
<td>3.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Total CO2 (mmol/L)</td>
<td>20-31</td>
<td>25</td>
<td>21</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>99-109</td>
<td>78</td>
<td>91</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>3.2-8.2</td>
<td>6.7</td>
<td>2.8</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Creatinine (umol/L)</td>
<td>44-71</td>
<td>40</td>
<td>31</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>Osmolality (mmol/kg)</td>
<td>275-295</td>
<td>237</td>
<td>256</td>
<td>248</td>
<td>267</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Osmolality (mmol/kg)</td>
<td>50-1200</td>
<td>459</td>
<td>399</td>
<td>463</td>
<td>387</td>
</tr>
<tr>
<td>Spot urinary sodium (mmol/L)</td>
<td>204</td>
<td>169</td>
<td>198</td>
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</tr>
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</table>
should be avoided. Any underlying infection and hypocaloric diet must be treated and corrected.\(^3\) In view of this, our patient was started on a high carbohydrate diet. Administration of intravenous haemin which inhibits ALAS transcription is the treatment of choice. However, haemin is not available in our centre.

CONCLUSION

Acute intermittent porphyria is a rare cause of severe hyponatraemia. It is believed to be the result of inappropriate secretion of anti-diuretic hormone. A high degree of clinical suspicion is required to establish the diagnosis of AIP. It should be considered in a patient presenting with persistent abdominal pain, intractable hyponatraemia and neurological symptoms.

ACKNOWLEDGEMENT

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REFERENCES