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Case Report

Acute intermittent porphyria with syndrome of inappropriate antidiuretic hormone secretion (SIADH) and neurological crisis, successfully treated with haemodialysis

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ABSTRACT

We report a 35 years old male, a case of Acute Intermittent Porphyria (AIP) with Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) and neurological crisis for its rarity. Since specific parenteral medication (hemin) was not available, patient was empirically treated with haemodialysis with satisfactory outcome.

Keywords: Acute porphyria, Antidiuretic hormone, Hyponatremia

INTRODUCTION

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a rare manifestation of AIP and very few cases have been reported in literature.[1,4] The major neurological manifestations of the acute porphyrias include neuropathic abdominal pain, peripheral neuropathy and mental changes.[2] Acute intermittent porphyria (AIP) is an autosomal dominant disorder resulting from a partial deficiency of porphobilinogen deaminase (PBGD) activity, the third enzyme in the pathway of heme synthesis.[2] The deficiency leads to increased blood levels of porphobilinogen (PBG) and decrease in heme synthesis. The deficiency of heme activates enzyme aminolevulinic acid (ALA) synthase, resulting in marked increase in ALA production.

CASE REPORT

Thirty five years old male was admitted to this rural hospital with history of altered sensorium since 9 days preceded by vomiting 10 days prior to hospitalization. Following this, he was hospitalized in private nursing home and was detected to have severe hyponatremia (serum sodium-108 mEq/L) where he received intravenous infusion of 3% saline without significant improvement. Since hyponatremia did not improve and his condition continued to deteriorate; he was referred to our hospital for evaluation and management of hyponatremia.

On examination, he was drowsy, disoriented and unresponsive to verbal command. His pulse was 112/minute and regular, blood pressure was 140/90 mmHg and respiratory rate was 24/minute. He had mild pallor and jugular venous pressure was normal. Cardiovascular examination revealed tachycardia and respiratory examination was normal. Abdomen was soft and there was no organomegaly. Laboratory investigations were as follows: urinalysis - normal. Blood urea- 26 mg/dl, serum creatinine - 0.8 mg/dl, serum sodium - 102 mEq/L, serum potassium - 5.1 mEq/l, serum chloride - 78 mEq/L and serum bicarbonate- 24 mEq/L, serum uric acid - 3.0 mg/dl, serum T4 - 1 ng/dl, serum TSH - 04 IU/ml, blood glucose - 104 mg/dl, serum protein- 6.8 gm/dl, serum albumin - 3.4 gm/dl, serum

calcium - 8.9 mg/dl, serum inorganic phosphorous - 2.0 mg/dl, serum magnesium - 1.7 mg/dl, serum bilirubin - 0.9 mg/dl, serum alkaline phosphate -357 IU/L, serum ALT - 100 IU/L, haemoglobin -10.5 g/dl, WBC count - 12,600/c.mm (neutrophil-74%, lymphocyte-21%, eosinophil-3%, monocyte-2%) and platelet count-151,000/c.mm. ANA and anti-ds-DNA were negative. The serum osmolality was 230 mOsm/kg, urine osmolality was 934 mOsm/kg and urinary sodium excretion was 100 mEq/day. In view of low serum osmolality, high urine osmolality, euvolemia, hyponatremia and urine sodium >25 mEq/L, the diagnosis of SIADH was considered. The magnetic resonance imaging (MRI) study of the brain was normal. He was given 500 ml of 3% saline and 40 mg of intravenous furosemide over 20 hours, following which serum sodium increased to 120 mEq/L and his sensorium improved. He was fed through naso-gastric tube and fluid intake was restricted to 500 ml per day. He was given 400 ml of 3% saline and 40 mg furosemide per day for the next three days. The serum sodium improved to 130 mEq/L after 72 hours. The serum sodium was frequently monitored and at no time rise in serum sodium was more than 10 mEq/L per day. Subsequently his neurological status worsened inexplicably despite considerable improvement in serum sodium (120 to 130 mEq/L). He developed three episodes of generalized tonic-clonic seizures following which he received intravenous phenytoin 1000 mg and sodium valproate 500 mg. However over the next 24 hours, his neurological status deteriorated rapidly. The MRI scan of brain was repeated and was normal. The cerebrospinal fluid analysis was normal. At this point, acute intermittent porphyria was suspected to be the cause of SIADH. The 24-hour urine collection was done via bladder catheterization. The urinary PBG was 8.5 mg/day (normal: <2 mg/day) and ALA was 280 mg/day (normal : <8 mg/day), both of which were markedly elevated, confirming the diagnosis of AIP causing SIADH. Phenytoin and sodium valproate were withdrawn, as they are known to precipitate an attack of AIP. He received 25% dextrose intravenous infusion for 72 hours and sensorium improved only marginally. Since injection hemin was not available and patient's condition was critical, after explaining the experimental nature of the treatment to the patients' relatives, he was given haemodialysis through jugular catheter for 7 consecutive days. Ignacy et al.[3,6] reported a case wherein neurological crisis in AIP was successfully treated with haemodialysis. The dialyzate sodium concentration was kept low at 130 mEq/L, to avoid rapid rise in serum sodium. The duration of dialysis was restricted to three hours for the first dialysis and subsequently increased to five hours. The spent dialysate was collected to estimate PBG and ALA concentration. The dialysis using low flux dialyzer was able to remove 1.5 mg of PBG and 232 mg of ALA per hour. His neurological status improved remarkably after 7 sessions of haemodialysis given on consecutive days. He regained conscious, oriented and was able to walk without support. Since injection hemin was not available even after one week of the diagnosis, biweekly haemodialysis was continued till four weeks and thereafter he was discharged when he fully recovered clinically and biochemically . He was normal at the time of discharge and had no neurological abnormality. The serum sodium was 136 mEq/L one month later and he remains well 12 months after the neurological crisis.

DISCUSSION

The clinical expression of the disease AIP is usually linked to factors that stimulate or depress the activity of the nonspecific delta-aminolevulinic acid synthase (ALAS1 or ALAS-N) in the liver.[1] The treatment of AIP is essentially non-specific and delay in treatment can result in irreversible neurological damage. Increased calorie intake and administration of heme analogue such as hemin and heme arginate are known to abate an acute attack of AIP by repressing ALAS-N activity.[2]

The mechanisms of neurological damage in AIP are not well understood and it is presumed that symptoms result primarily from the porphyrin precursors themselves rather than a deficiency of heme in nerve tissue.[2,3,6] However it appears that ALA may be the neurotoxin responsible for the majority of neurological manifestation in AIP. AIP is a rare condition with reported incidence of 1-2 per 100000 in Europe.[2,6,] However its true incidence in Indian subcontinent is unknown. Less than two hundred cases of AIP have been reported from India and approximately 70% of these cases are from a community in the state of Rajasthan. Approximately 80% of individuals with this inherited enzyme deficiency remain biochemically and clinically normal throughout life.[2] The attacks in AIP may be precipitated by vast array of drugs, chemicals, starvation, alcohol and smoking. Few cases of SIADH due to involvement of hypothalamus in AIP have been reported in literature.[2,4] Our patient presented with gastrointestinal symptoms, mild psychiatric symptoms and severe symptomatic hyponatremia due to SIADH. The diagnosis of AIP was confirmed by demonstration of marked increase in urinary PBG and ALA. Our patient fulfilled all the criteria for diagnosis of SIADH and the cause could be clearly attributed to AIP. He developed seizures despite improvement in serum sodium and neurological condition worsened following administration of phenytoin and sodium valproate, both of which are known to precipitate an attack of AIP. As there was delay in obtaining heme analogue due to non-availability, we subjected him to haemodialysis to remove PBG and ALA. The analysis of spent dialyzate showed that dialysis was very effective in removing these small molecular weight substances. One hour of low flux dialysis removed 1.5 mg of PBG and 232 mg of ALA, which is 18% and 48% respectively of what was excreted in the urine over 24 hours. There was a remarkable improvement in neurological status following seven sessions of haemodialysis done on consecutive days. There have been previous reports of attempt to treat an

attack of AIP with extracorporeal therapies, showing significant results.[5,6] Ignacy et al. reported a case of a woman with severe acute intermittent porphyria, in whom routine pharmacological treatment was unsuccessful and after five haemodialysis sessions, a dramatic improvement in the clinical status was observed.[5]

Based on our experience, we recommend that haemodialysis may be used to treat an attack of AIP in case heme analogue is not available or as an adjunct therapy along with heme analogue for rapid resolution of an attack of AIP. In view of easy dialyzability of PBG and ALA, one could speculate that slow prolonged dialysis or continuous renal replacement therapies may be used, in case there is a rapid rebound in the blood concentration of these toxins.

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