The Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) and Neurological Crisis due to Acute Intermittent Porphyria, Successfully Treated with Haemodialysis

RA Annigeri*, VM Ganesan**

Abstract
We report an eighteen year old female, a case of acute intermittent porphyria with syndrome of inappropriate antidiuretic hormone secretion, as presenting feature for its rarity. The neurological crisis was successfully treated with haemodialysis. ©

INTRODUCTION
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. 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. The major manifestations of the acute porphyrias are neurologic which include neuropathic abdominal pain, peripheral neuropathy and mental disturbances. The syndrome of inappropriate secretion of antidiuretic hormone secretion (SIADH) is a rare manifestation of AIP and very few cases have been reported in English literature.

CASE REPORT
Eighteen years girl was admitted to the hospital with history of altered sensorium since 7 days. She developed vomiting 10 days prior to hospitalization and three days later became drowsy. Following this, she was hospitalized elsewhere and was detected to have severe hyponatremia (serum sodium-110 mEq/L). She received intravenous infusion of 3% saline. Since hyponatremia did not improve and she became increasingly drowsy, she was referred to our unit for evaluation and management of hyponatremia. The previous history revealed that she had recurrent episodes of vomiting lasting for 4-5 days, typically occurring in the premenstrual period for last 8 months. In recent months, her parents had noticed a marked decline in her academic performance. She also exhibited fear and anxiety over trivial matters.

On examination, she was drowsy, disoriented, did not obey verbal commands and had withdrawal response to tactile stimulus. Glasgow coma scale (GCS) score was 7. Her pulse was 110/minute, blood pressure was 150/100 mmHg and respiratory rate was 26/minute. She had mild pallor, no edema and jugular venous pressure was normal. Cardiovascular examination revealed tachycardia and respiratory examination was normal. Abdomen was soft, there was no organomegaly and bladder was not palpable. Laboratory investigations were as follows: Urine albumin-trace, occasional RBC and 1-2 WBC/hpf, blood urea- 20 mg/dl, serum creatinine- 0.5 mg/dl, serum sodium- 100 mEq/L, serum potassium- 5.0 mEq/l, serum chloride- 75 mEq/L and serum bicarbonate- 20 mEq/L, serum uric acid- 2.0 mg/dl, serum T4- 1 ng/dl, serum TSH- 0.4¼ IU/ml, blood glucose- 103 mg/dl, serum protein- 6.9 gm/dl, serum albumin- 3.4 gm/dl, serum calcium- 7.9 mg/dl, serum inorganic phosphorous- 2.0 mg/dl, serum magnesium- 1.8 mg/dl, serum bilirubin- 0.9 mg/dl, serum alkaline phosphate- 377 IU/L, serum ALT- 126 IU/L, heamoglobin-10.5 g/dl, WBC count- 14,600/c.mm (neutrophil-84%, lymphocyte- 11%, eosinophil-3%, monocyte-2%) and platelet count- 161,000/c.mm. ANA and anti ds-DNA were negative. The serum osmolality was 220 mOsm/kg, urine osmolality was 544 mOsm/kg and urinary sodium excretion was 102 mEq/day. In view of low serum osmolality, high urine osmolality, euvoolemia, hypouricemia and urine sodium >25 mEq/L, the diagnosis of SIADH was made. The magnetic resonance imaging (MRI) study of the brain was normal. She was given 600 ml of 3% saline and 60 mg of intravenous furosemide over 24 hours, following which serum sodium increased to 108 mEq/L and her sensorium improved (GCS score-10).
She was fed through naso-gastric tube and fluid intake was restricted to 500 ml per day. She was given 300 ml of 3% saline and 40 mg furosemide per day for the next two days. The serum sodium improved to 120 mEq/L after 72 hours. The serum sodium was frequently monitored and at no time rise in serum sodium was more than 8 mEq/L per day. Subsequently her neurological status worsened inexplicably despite considerable improvement in serum sodium (115 to 120 mEq/L). She developed two episodes of generalized tonic-clonic seizures following which she received intravenous fosphenytoin 300mg and sodium valproate 400 mg. However over the next 12 hours, her neurological status deteriorated rapidly and GCS score decreased to 6. 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 8.2 mg/day (normal: <2 mg/day) and ALA was 488 mg/day (normal: <8 mg/day), both of which were markedly elevated, confirming the diagnosis of AIP causing SIADH. Fosphenytoin and sodium valproate were withdrawn, as they are known to precipitate an attack of AIP. She received 25% dextrose intravenous infusion for 36 hours and sensorium improved only marginally (GCS score-8). Despite extensive search, injection hemin was not available anywhere in India. Ignacy et al5 reported a case wherein neurological crisis in AIP was successfully treated with haemodialysis. As the patient’s condition was critical, after explaining the experimental nature of the treatment to the parents, she was given haemodialysis through jugular catheter for 5 consecutive days. The dialyzed 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 four 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 (simultaneous dialysis urea clearance was 80 ml/minute). Her neurological status improved remarkably after 5 sessions of haemodialysis given on consecutive days. She was conscious, oriented and was able to walk with support (GCS score-14). Injection hemin was made available a week after making the diagnosis. Haemodialysis was discontinued and she was given 180 mg (4 mg/kg) of intravenous hemin daily for two consecutive days. She was normal at the time of discharge 5 days after administration of hemin and had no neurological abnormality. The serum sodium was 130 mEq/L one month later and she remains well 12 months after the neurological crisis. Her elder brother presented six months later with acute abdominal pain which subsided with conservative measures. On evaluation he was found to have high urinary excretion of PBG and ALA confirming the diagnosis of AIP in him.

**DISCUSSION**

AIP is a rare condition with reported incidence of 1-2 per 100,000 in Europe.1 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.1 The attacks in AIP may be precipitated by vast array of drugs and chemicals, starvation, alcohol, smoking and pre-menstrual hormonal changes in women. The clinical expression of the disease 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.1

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.1 However it appears that ALA may be the neurotoxin responsible for the majority of neurological manifestation in AIP. In a rare condition of ALA porphyria, wherein deficiency of ALA dehydratase causes increased levels of ALA, but not PBG produce a neurological disease indistinguishable from AIP.

Few cases of SIADH due to involvement of hypothalamus in AIP have been reported in English literature.2-4 Our patient presented with gastrointestinal symptoms typically occurring in pre-menstrual period, 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. She developed seizures despite improvement in serum sodium and neurological condition worsened following administration of fosphenytoin and sodium valproate, both of which are known to precipitate an attack of AIP. The neurological crisis did not improve following dextrose infusion. As there was delay in obtaining heme analogue due to non-availability, we subjected her to haemodialysis to remove PBG and ALA. The analysis of spent dialysate 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 five sessions of haemodialysis done on consecutive day (GCS score improved from 8 to 14). There have been two previous reports of attempt to treat an attack of AIP with extracorporeal therapies, showing contrasting results.5,6 Ignacy et al5 reported a case of a woman with severe acute intermittent porphyria, in whom routine pharmacological
treatment was unsuccessful. After five haemodialysis sessions a dramatic improvement in the clinical status was observed. However, Laiwah et al\textsuperscript{6} used charcoal haemoperfusion in series with haemodialysis for two hours daily for four consecutive days in a patient with AIP. Although during treatment serum and urinary concentration of PBG and ALA were considerably reduced, they returned to pretreatment values after the end of the treatment. There was no relief of abdominal pain. The authors felt that even longer dialysis sessions may not have helped as the ALA and PBG levels rebound rapidly after treatment.

Our case was unique in several ways: firstly severe hyponatremia due to SIADH was the presenting feature of AIP; secondly acute attack of AIP was successfully treated with haemodialysis and thirdly, effective removal of PBG and ALA on haemodialysis was documented by measuring their concentration in spent dialyzate. 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.

In conclusion, we report SIADH with severe symptomatic hyponatremia in an 18 years female, which unmasked underlying cause due to AIP. The neurological crisis was successfully treated with haemodialysis and efficient removal of PBG and ALA was demonstrated by analyzing spent dialyzate.

REFERENCES