Case Report

Abstract

Porphyrias are a group of rare metabolic diseases that result from enzymatic defects of porphyrins metabolism and heme synthesis. Accumulation of porphyrins and their precursors present with neuro-visceral symptoms and/or skin lesions. Acute porphyrias may have variety of manifestations; most common of them are abdominal pain and central nervous system disturbances, hyponatremia is highly characteristic for acute intermittent porphyria and is usually attributed to syndrome of inappropriate secretion of antidiuretic hormone (SIADH). We present here three cases of acute porphyria, primary diagnosed in ICU by nephrologist, invited for evaluation and treatment of severe hyponatremia and discuss causes of hyponatremia, differentiating between SIADH and cerebral salt wasting (CSW) syndrome.

Keywords: Acute porphyria; Clinical; Electrolyte imbalance

Abbreviations: ALA: Amino Levulonic Acid; AlAT: Alanine Amino Transferase; AsAT: Asparagine Amino Transferase; AVP: Arginine-Vasopressin; BP: Blood Pressure; Ca: Calcium; CK: Creatine Phosphokinase; Cl: Chloride; CSW: Cerebral Salt Wasting; CT: Computer Tomography; ECG: Electrocardiogram; ECHO-CG: Echocardiography; Hb: Hemoglobin; HPF: High Power Field; HR: Heart Rate; K: Potassium; LDH: Lactate Dehydrogenase; LP: Lumbar Punction; Na: Sodium; NSAID’s: Nonsteroid Anti-Inflammatory Drugs; O2 Sat: Oxygen Saturation; PBG: Porphobilinogen; Plt: Platelets; Posm: Plasma Osmolality; RBC: Red Blood Cells; RR: Respiratory Rate; SIADH: Syndrome of Inappropriate Secretion of Antidiuretic Hormone; SG: Specific Gravity; TB: Total Bilirubin; TBC: Total Blood Count; TP: Total Protein; UTI: Urinary Tract Infection; WBC: White Blood Cells

Introduction

The Porphyrias are a group of rare metabolic diseases that result from defects (genetic or, rarely, acquired) of enzymes needed at various steps of heme synthesis. As precursors of heme are porphyrins, deficiencies in any of enzymes, involved in their metabolism, may lead to the accumulation of porphyrins, presenting with distinct clinical syndromes- acute or chronic. Porphyrias are also classified into those predominantly involving the skin, those manifesting as disorders of the liver/nervous system, and a combination involving all 3 entities. Clinical manifestations depend on the particular enzymatic defects -if the defects are in the initial steps of the metabolic cascade, neurotoxic early metabolic intermediate products (i.e. amino Levulonic acid and Porphobilinogen) accumulate, resulting with attacks of neurologic dysfunction; if the defects are in the final steps, porphyrin accumulate in the skin causing photosensitivity. The acute porphyrias are characterized by periodic acute attacks of eurovisceral symptoms. This group include acute intermittent porphyria, the Doss porphyria, hereditary coproporphyria, and variegate porphyria. The chronic porphyrias (congenital erythropoietic porphyria, erythropoietic porphyria, and poorthyria cutanea tarda) are dermatologic diseases that may or may not involve the liver and nervous system and do not present with acute attacks [1-3].

Acute porphyria clinical presentation may include:

I. Abdominal pain
II. Constipation/diarrhoea
III. Nausea/vomiting
IV. Arterial hypertension/tachycardia
V. Fever
VI. Sweating
VII. Muscle weakness
VIII. Tetraparesis
IX. Respiratory paralysis
X. Limb pain
XI. Motor neuropathy
XII. Paresthesias/dysesthesias, numbness
XIII. Cranial nerve involvement/blindness
XIV. Tremor
XV. Seizures
XVI. Urinary retention/incontinence, dysuria
XVII. Aphasia/apraxia
XVIII. Psychosis
XIX. Anxiety/restlessness
XX. Agitation
XXI. Confusion/coma
XXII. Depression/insomnia
XXIII. Skin rush
XXIV. Rhabdomyolysis
XXV. Red/brown urine
XXVI. Elevated WBC count
XXVII. Hyponatremia

Keywords: Acute porphyria; Clinical; Electrolyte imbalance
Acute intermittent porphyria is the most common and the most severe form of the inherited hepatic porphyrias, affecting mainly young women. Provoking factors are known to be alcohol ingestion, infection, surgical procedure, variety of drugs, low-carbohydrated diet or fasting and menstruation [4-11]. We present three cases of newly diagnosed acute porphyria, presenting with severe hyponatremia in ICU.

Case 1

Nephrologist was invited to ICU to consult the patient with hyponatremia (Serum Na 103 mmol/l). Caucasian lady 29 years old, day 6 in the hospital, day 2 in ICU.

Physical examination

Erythematos face rash, lips red boarder bright, no edema, skin and mucous dry. Coma, motor excitement, adequate pain reaction, lack of swelling, normal cough reflex, widened pupils with normal photo reactivity. Body temperature 37.0°C, apsontaneous respiration, RR 25 per minute, HR140 per minute, BP160/85 mm Hg. Heart and lung unremarkable, abdomen soft, non-tender. Stool after enema, normally colored, urination via ureteral catheter, urine colored reddish-brown, urine output 4800 ml/day.

Workup

HB 15.6g/dl, WBC 12.9x10^6/mcl, Plt127x10^6/mcl, TP 6.2 g/dl, TB 20 mc mol/l, creatinine 66 mc mol/l, urea 4.9 mmol/l, uric acid 189 mc mol/l, AsAT 137U/l, ALAT66 U/l, amylase 218U/l, CK25899U/l, LDH 650 U/l, K 2.8mmol/l, Na 103mmol/l, Ca++ 0.97mmol/l, Cl 73 mmol/l, Posm 214 mosm/kg, pH 7.55, bicarbonate 25.3 mmol/l, 02sat 91% at room air.

LP

Liquor colorless, transparent, protein 1.1 g/l, neutrophil cytosis 15/3.

Urinalysis

Protein 0.5 g/l, glucose-abs, WBC 3-4, RBC 1-2 HPF, bilirubin+++, urobilin+++.

Previous medical history

Unremarkable-nothing but normal pregnancy 5 years ago. She was known to have respiratory symptoms, chill, fever (38.6°C) and myalgia6 days before admission, and taking paracetamol and antibiotics. In two days respiratory symptoms resolved, but she experienced abdominal pain, vomiting, constipation, and noticed dark urine.

Clinical Course

3 days later, with the same complains she was seen in ER of our hospital. Physical examination did not show anything significant. Workup, including standard labs, ECG, ultrasound, chest and abdomen plain X-ray, radio contrast kidney X-ray and laparoscopy found nothing but “reddish-brown” urine (protein 0.033 g/l, RBC 70-80 hpf), mild hyponatremia (133 mmol/l), and sinus tachycardia. She was diagnosed with UTI, referred to urology unit and started with NSAID’s, antiemetic’s, spasmolytics, Ringer solution, cephalosporin’s, antifungal and omeprazole.

Day 3 in the hospital fever resolved, but she complained for dysuria and severe back pain, which were interpreted as a consequence of her regular menses, Novocain was added to her treatment. Day 5 she was found depressed, and started with amitriptyline, the same night she developed seizures (treated with carbamazepine and diazepam), and coma. CT showed brain edema, and she was transferred to ICU and continued withdiazepam, carbamazepine, omeprazole, cephalosporins and normal saline; potassium chloride and magnesium were added.

Diagnosis and Follow-up

Day 6 (day 2 in the ICU) her neurologic status was unchanged, hemodynamics-stable, but respiratory distress worsened. Given skin lesions, abdomen pain and constipation, seizures, coma, dark urine (Figure 1), and hyponatremia - nephrologist suspected acute porphyria. High CK and LDH were attributed to rhabdomyolysis. Additional workup, including urine Ehrlich test for porphyrins was recommended, and it was advised to discontinue magnesium, antibiotic’s and anticonvulsant’s, and infuse NaCl 3% solution 1-2 ml/kg/hour under serum sodium control, targeting sodium not higher than 115-116 mmol/l at the end of first day.

Day 8 (day 4 in ICU) patient’s condition improved. Spontaneous respiration, conscious, but confused, BP 140/80 mmHg, HR120 per minute. Plasma Na-122mmol/l, urine output 2600 ml/24 hours, urine still reddish-brown (Figure 1), and Ehrlich test-positive. Diagnosis of acute porphyria with first clinical manifestation after viral infection, menstruation, and NSAIDS, antibiotics and sedatives usage was confirmed. Day 10 (day 6 in ICU) she was stable, slightly confused, BP 135/85 mm Hg, HR 110 per minute. Plasma Na 129mmol/l K 4.1mmol/l, Ca++ 1.28mmol/l, Cl 104 mmol/l, pH 7.38. Patient was transferred to reference centre for Porphyrias.

Case 2

Nephrologist was invited to ICU to consult the patient with hyponatremia (serum Na 114mmol/l). Caucasian lady 30 years old, day 10 in the hospital, day 2 in ICU.

Main complains

Weakness, pain in her neck, back and lower extremities and lower extremities numbness.

Physical examination

Lips red boarder bright, erythematous rush on her face, neck and upper extremities (Figure 2), no edema, skin and mucous dry.
Conscious, slightly confused, no focal signs. Body temperature 37.2°C, spontaneous respiration, RR 20 per minute, HR 78 per minute, BP 150/80 mm Hg. Heart and lung unremarkable, abdomen soft, non-tender. No stool. Spontaneous urination with red urine, urine output was 2500 ml/day.

Workup

Hb 14.0 g/dl, WBC 9.8x10^6/mcl, Plt 295x10^6/mcl, TP 6.0g/dl, albumin 3.6 g/dl, TB 25 mc mol/l, creatinine 0.02 m mol/l, urea 4.0 m mol/l, AsAT 64 U/l, ALAT 27 U/l, amylase 117 U/l, CK 324 U/l, LDH 257 U/l, K 2.3 m mol/l, Na 114 m mol/l, Cl 84 m mol/l, Posm 241 mosm/kg, pH 7.56, bicarbonate 30.6 m mol/l, O2 sat 100% at room air.

Urinalysis

Protein 0.7 g/l, bilirubin 34 mmol/l, urobilin 50 mmol/l, WBC, RBC – 0-1 hpf, urine osmolality 316 mosm/kg.

Previous medical history

2 normal pregnancies 7 and 5 years ago. 9 months before current episode, after taking vermicides (together with her kids who had seat worms), she developed severe abdominal pain and pain in lower extremities and was admitted to local hospital. She got laparotomy, which did not show any surgical disease. 3 months later she had another episode of abdominal pain, recognised as adhesive obstruction and resolved without surgery.

At the day of admission she developed abdominal pain and 6 hours later was admitted to surgery unit of our hospital, suspected for appendicitis. Her vital signs were otherwise normal, abdomen soft and non-tender; slightly painful in epigastrium and right flank.

Clinical course

Normal TBC and blood chemistry but plasma Na 133 mmol/l, and normal urinalysis. ECG showed sinus tachycardia. Abdomen and pelvic ultrasound and plain abdomen X-ray were normal, small bowel follow through showed ileocecal barium retention; she was diagnosed with adhesive obstruction and treated with normal saline, Ringer solution and spasmyotics.

Day 3 of hospital stay she still had diffuse abdominal pain and complained for pain in lower extremities, her vital signs, stool and urination were normal. TBC was normal with Hb 16.0 g/dl, blood chemistry found TB 28 mc mol/l, creatinine 84 mc mol/l, urea 2.2 mmol/l, AsAT 66 U/l, Na 130 mmol/l, K 4.4 mmol/l, Cl 90 mmol/l. Urinalysis: SG 1015, protein absent, bilirubin 8.5 mmol/l, gastroscopy revealed reflux-gastritis, colonoscopy showed only dolychosigmoid. She was continued with normal saline, Ringer solution and spasmyotics, NSAID’s were added.

Day 7 of hospital stay she complained skin rush and developed agitation, neurologist did not find any focal signs and diagnosed neurotic reactions, sulpiride was added. Dermatologist diagnosed toxicodermia and recommended to continue crystalloid infusions. Day 9 of hospital stay her condition worsened, she complained of pain in her neck, back and lower extremities, found to be hypovolemic and confused, referred to ICU and continued with normal saline, Ringer solution, omeprazole and NSAID’s, cephalosporin’s, amino glycoside’s, calcium-channel blockers, beta-blockers, ACE-inhibitors, heparin and diazepam were added.

Diagnosis and follow-up

Day 10 (day 2 in ICU) her condition did not changed. Nephrologist, basing on 3 episodes of abdominal pain, laparotomy with uncertain diagnosis 9 months ago, skin rush, neck, back and low extremities pain, arterial hypertension and tachycardia, agitation, numbness, red urine and hyponatremia suspected acute porphyria. It was advised to perform urine Ehrlich test for porphyrins, discontinue antibiotics, heparin, diazepam, NSAID’s, antihypertensive’s, and infuse Glucose 40% 1000 ml/day and NaCl 3% solut on 1-2 ml/kg/hour under serum sodium control, targeting sodium not higher than 125 mmol/l at the end of first day.

Day 12 of hospital stay (day 4 in ICU) patient’s condition improved - conscious, alert, no focal signs, mild pain and numbness in lower extremities. Vital signs normal, urine output 2000 ml/day. Normal stool. Plasma Na 129 mmol/l, K 4.1 mmol/l, CK 346 U/l. Ehrlich test – positive. Diagnosis of acute porphyria was confirmed and patient was transferred to reference centre for Porphyrias.

Case 3

Nephrologist was invited to ICU to consult the patient with hyponatremia (serum Na 112 mmol/l). Caucasian lady 39 years old, day 4 in the hospital, day 2 in ICU. Sopor, no focal signs.

Physical examination

Figure 3: Case 2-skin rush.
Erythematous skin rush (Figure 3) and hyperpigmentation on upper extremities, no edema, skin and mucous dry. Body temperature 36.6°C, spontaneous respiration, RR 22 per minute, HR 80 per minute, BP 135/80 mmHg. Lung and heart unremarkable, abdomen soft, not tender. No stool, urination via urethral catheter, urine colored dark brown, and urine output 4300 ml/day.

**Workup**

HB 13.0 g/dl, WBC 6.6x10^6/mcl, PIt 307x10^6/mcl, TP 6.5 g/dl, TB 23mcmol/l, albumin 3.5 g/dl, creatinine 81 mcmol/l, urea 3.8 mmol/l, AsAT 23 6U/l, AIAT 81 U/l, amylase 102 U/l, CK 9570 U/l, LDH 379 U/l, K 2.9 mmol/l, Na 112 mmol/l, Cl 85 mmol/l, Posm 231 mosm/kg, pH 7.49, bicarbonate 20.4 mmol/l, O2 sat 100% at room air.

**Urinalysis**

SG 1015, protein abs, bilirubin 34 mmol/l, urobilin 34 mmol/l, WBC, RBC-absent. ECG showed sinus tachycardia and ST elevation in 2nd standard lead, ECHO-CG revealed left ventricular dilatation and anteroseptal hypo kinesis with ejection fraction 42%.

**Previous medical history**

Normal pregnancy 14 years ago, since that time she was taking oral contraceptives. 3 years ago she had anepisodes of abdominal pain; laparotomy did not show any surgical disease. 2 weeks before current admission she developed abdominal pain, was admitted to the surgery unit our hospital, complaining for constipation, and diagnosed with abdominal colic. Her vital signs were otherwise normal, abdomen, slightly painful but soft and non-tender. Workup showed normal TBC, blood chemistry revealed total bilirubin 40 mmol/l, AsAT 166 U/l, AIAT 98 U/l, cholesterol 8.3 mmol/l, K 3.9 mmol/l, Na 106 mmol/l, other test were normal. Urinalysis was not performed. ECG, abdomen and kidney ultrasound, chest and abdomen plain X-ray, abdomen CT and colonoscopy were unremarkable. She was seen by neurologist and diagnosed with asthenia. She received spasmolytics and laxative's, her condition improved and she was seen by neurologist and diagnosed with asthenia. She received spasmolytics and laxative's, her condition improved and she was transferred to reference centre for Porphyrias.

**Clinical course**

HB 12.9 g/dl, WBC 5.0x10^6/mcl, PIt 230x10^6/mcl, TB 9 mcmol/l, creatinine 71 mcmol/l, urea 2.6 mmol/l, AsAT 84 U/l, AIAT 57 U/l, amylase 157 U/l, K 4.8 mmol/l, Na 129 mmol/l, Ca++ 1.1 mmol/l, Cl 100 mmol/l; urinalysis: SG 1010, protein-abs, bilirubin 8.5 mmol/l, WBC, RBC-absent. Plain chest, abdomen and kidneys X-ray, abdomen and kidneys ultrasound-otherwise normal but mild pancreatic hypechoogenicity. She was diagnosed with pancreatitis, referred to surgery unit and treated with normal saline, Ringer solution, NSAID's, spasmolytics, and omeprazole; heparin was added.

**Brain CT** did not show anything significant, she was diagnosed with "toxic psychosis", referred to ICU and continued with normal saline, Ringer solution, NSAID's, cephalexin and omeprazole; heparin was added.

**Diagnosis and follow-up**

Day 4 (day 2 in ICU) her vital signs were stable, but she became soporos. Nephrologist, basing on prolonged usage of oral contraceptives, laparotomy for uncertain indications 3 years ago, abdominal pain, constipation, nausea, vomiting, psychosis and hyponatremia suspected acute porphyria. It was advised to perform urine test for porphyrins, discontinue antibiotics, NSAID's and heparin, and infuse Glucose 40% 1000 ml/day and NaCl 3% solution 1-2 ml/kg/hour under serum sodium control, targeting sodium not higher than 120 mmol/l at the end of first day.

Day 5 (3 day in ICU) her condition improved-conscious, alert, no focal signs. Vital signs normal, urine output 6200 ml/day. Stool after enema, normally coloured. Plasma Na 125 mmol/l, K 4.7 mmol/l, CK 1448 U/l, LDH 574 U/l. Urine test for porphyrins: Total porphyrins 0.29 mg/l, PBG 81 mg/ml, ALA 21 mg/ml. Diagnosis of acute porphyria was confirmed and patient was transferred to reference centre for Porphyrias.

**Discussion**

All three cases, we present here, show typical manifestations of acute porphyria with numerous abdominal and central nervous system symptoms, rhabdomyolysis, and coloured urine, and also with skin lesions in two cases. Female sex and young age, as well as trigger factors like infection, menstruation and various medications is very common in acute porphyria. Misdiagnosing, laparotomy and treatment with NSAID’s, antibiotics and sedatives, which lead to the deterioration of patients condition, is also characteristic for cases of acute intermittent porphyria before proper diagnosis is made [12-18].

Marked hyponatremia, which is most common electrolyte imbalance in patients with neurologic diseases, frequently complicates acute porphyrias. Its mechanism is not fully understood, but SIADH, gastrointestinal losses, infusions of hypotonic dextrose-containing fluids, nephrotoxicity, excess renal sodium excretion, and damage to the supraoptic nuclei of the hypothalamus, has been implicated in its pathogenesis [16,17,19-27].

We considered SIADH, but some clinical data could not be completely understood in this setting. SIADH is volume expanded status due to increased renal water reabsorption by excessive and inappropriate AVP secretion, often seen in patients with central nervous system diseases and hyponatremia. But many of these patients, who meet the diagnostic criteria for SIADH, have a volume status incompatible with that diagnosis. The evidence of volume depletion in these patients is more consistent with the diagnosis of CSW syndrome. CSW syndrome is characterized by excess renal sodium wasting with resulting volume depression. Although, the mechanism of CSW syndrome is not fully understood, the most possible hypothesis is central amplification of natriuretic peptides, especially brain natriuretic peptide, combined with decreased sympathetic outflow due to various neurologic diseases. SIADH and CSW syndrome are...
two main mechanisms of hyponatremia in patients with various neurologic diseases, excluding iatrogenic causes. Distinction between SIADH and CWS syndrome may be difficult due to overlapping laboratory findings and clinical presentations, the fundamental differences between these two entities are as follows: SIADH is in a volume expanded status due to inappropriately secreted AVP, however, CWS syndrome is in a volume depleted status characterized by renal sodium wasting and appropriate secretion of AVP [28-32].

In our three patients plasma osmolality was decreased to 214, 241 and 231mosm/kg respectively, but they all were volume depleted, with dry skin and mucosa, hemoglobin normal or as high as 16.0g/dl and urine output increased. Only one of our three patients had vomiting, not that much prolonged, and none of them were diarrheal. Also none got hypotonic glucose-containing infusions.

Conclusion

The main cause of severe hyponatremia in our patients was excess renal sodium excretion due to CWS syndrome, and we found only one case of similar findings explained by CWS syndrome in acute intermittent porphyria on Contemporary Pediatrics site: “A wild case of abdominal pain” by Georgy B. Kenny.

References

