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LEARNING POINTS FROM A DELAYED DIAGNOSIS OF PORPHYRIA

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ABSTRACT

A 26year male with no significant past medical history presented with complaints of abdominal pain, altered sensorium and seizure. Clinical examination was significant for a blood pressure of 160/90 mm Hg and diffuse abdominal tenderness. On detailed history, there was similar events in the past without any clear diagnosis even after extensive work up. Urine porphobilinogen test done earlier was negative, but it was done without proper urine collection methods. Serum cortisol was low along with low sodium, serum amylase was elevated on one occasion, all these led on to delay in diagnosis. Because of a high suspicion for acute intermittent porphyria (AIP), urine was tested for porphobilinogen (PBG) with proper care and came as positive. Patient was treated with glucose, electrolyte correction and other supportive measures with which he improved and was discharged home.

CASE PRESENTATION

26year old male with no significant past medical history came to the emergency department with complaints of abdominal pain and vomiting for 5 days, altered sensorium for 2 days. He had one episode of generalized tonic clonic seizure which lasted for about five minutes. On initial examination, his vitals showed blood pressure of 160/90 mmHg, pulse rate of 118/min, and he was saturating 96% on room air. He was agitated and disoriented. There was no neck rigidity or any focal neurological deficits, a but had diffuse tenderness per abdomen without any guarding or rigidity. His initial labs were pertinent for anemia, hyponatremia, hypoglycemia and mild elevation of amylase and lipase. He was admitted to the hospital with differential diagnoses which included pancreatitis as a cause of his abdominal pain, vomiting and the resultant hyponatremia as the cause of his seizures. Urine porphobilinogen test was negative. He was kept nil per oral, started on intravenous fluids and a bolus of 3% saline was given for the management of symptomatic hyponatremia. An initial USG Abdomen done on the day of admission was not contributory. His mentation improved the next morning and a more detailed history was taken from the patient and his relatives at bedside which uncovered two similar episodes in the past year. Investigations done are shown in table A:

Table A

	Patients values	Normal range
Total WBC count	11800 /microliter	5000-11000 /microliter
Hemoglobin	12 g/dl	13.5-17.5 g/dl
Platelet count	384000/microliter	150-450000/microliter
ESR	32 mm at 1hr	0-22 at 1 hr
RBS	24 mg/dl	70-100/dl
BUN/Creatinine	32/1.1 mg/dl	8-25 mg/dl/0.6-1.2mg/Dl
Serum Sodium	108 mmol/L	135-145 mmol/L
Serum Potassium	4.1 mmol/L	3.5-5.2 mmol/L
ALT/AST	30/14 IU/L	0-32 IU/L / 0-40 IU/L
Alkaline Phosphatase	69 IU/L	39-117 IU/L
Total Protein/Albumin	5.0/3.4 g/dl	6-8.5g/Dl / 3.5-4.8g/Dl
Urine Routine	Normal	
Serum Amylase	166 U/L	0-80 U/L
Serum Lipase	237 U/ L	0-60 U/L
TSH	0.6mIU/L	0.4-4.6mIU/L
FT3	2.1ng/dL	1.3-4.2ng/dL
FT4	1.7ng/dL	0.8-2.4ng/dL
Fasting Cortisol	13 mcg/dL	10-20 mcg/dL
Serum ACTH	4.91pg/ml	7.2-63.3pg/ml

DIAGNOSIS

He was evaluated extensively during his first admission which included brain imaging, lumbar puncture which were both negative. Hospital records showed low blood sugars, severe hyponatremia and fasting cortisol low normal which was considered as inadequate in a stressful state. He was discharged with a provisional diagnosis of adrenal insufficiency from the hospital on oral steroids. Three months from the initial event, patient was again admitted with similar complaints and was reported to have dark red colored urine. Before he could be evaluated further for his symptoms, patient left against medical advice and was lost to follow up. This time he was readmitted with abdominal pain and vomiting. In view of recurrent neurovisceral symptoms, Acute Intermittent Porphyria was high in our differentials along with the more common diagnoses such as recurrent attacks of chronic pancreatitis, alcohol withdrawal delirium. In addition, during the first episode he was reported to have fluctuating blood pressure, hyponatremia and inappropriately low fasting cortisol for the stress situation which raised the suspicion of Addison's disease causing his recurrent symptoms. Due to the strong clinical suspicion, the urine porphobilinogen test was repeated, this time with proper collection technique. This included the collection of freshly voided sample to a dark bottle and testing it without any time delay, fig[a] This time test came as positive for porphobilinogen and the patient was diagnosed to have Acute Intermittent Porphyria.

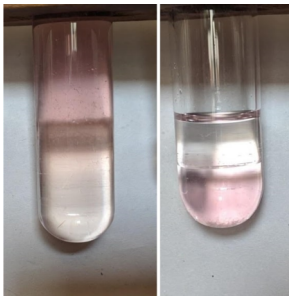

Figure a

Urine showing positivity for urine PBG by Watson and

Schwartz test Addition of Ehrlich reagent (paradimethyl amino benzaldehyde in hydrochloric acid) yields pink-red colour. Further addition of chloroform leads to 2 layer formation as PBG is insoluble in Chloroform (unlike UBG which is soluble and hence pink colour in bottom layer)(Test tube on left).Second extraction of aqueous layer done with butanol, here urine goes down as it is heavier than butanol (Test tube on right).

He was treated with intravenous glucose loading, high carbohydrate diet, hyponatremia correction. His condition improved with the above measures and got discharged from the hospital. He was advised to avoid alcohol and fasting and to ensure high carbohydrate food. At monthly follow up he was doing well and able to continue his work.

DISCUSSION

Derived from the Greek word porphura meaning purple, the Porphyrias are a group of disorders characterised by deficiency of specific enzymes in haem synthesis. Acute Intermittent Porphyria manifests due to deficiency of the enzyme hydroxymethylbilane synthase (PBG Deaminase) which converts Porphobilinogen (PBG) to Hydroxyme thylbilane.[1]

Neurological symptoms in this disease are believed to occur due to the toxic effects of the excess amino levulenic acid (ALA) formed from the block in the heme production pathway. Steroidal hormones, alcohol, drugs and starvation induce hepatic ALA synthase and notable causes for disease precipitation.

Acute attacks are characterised by autonomic symptoms that include tachycardia, labile blood pressure, severe abdominal pain resulting from visceral autonomic neuropathy.[2] Central nervous system involvement is characterised by confusion, seizures, coma.

The hallmark in diagnosis is the demonstration of porphyrin precursors in urine. Some of the tests that can be used for the purpose include ion exchange chromatography, Hoesch test, Watson and Schwartz test. The basic principle behind these tests is the conversion of colorless PBG in urine to porphyrins. However, this reaction can be impeded and may result in false negative results due from exposure of urine to light prior to testing .[3]

Preventive therapy in AIP includes avoidance of fasting, alcohol and medication that precipitates an attack. In case of acute attack, initial management is through narcotic analgesics for pain management and correction of fluid and electrolyte imbalance. Care must be taken in the choice of antiepileptics which is a major drug category that exacerbates the attacks. Milder attacks can be managed with dextrose infusion while more severe attacks warrant use of hemin. Hemodialysis has been described to have a role in severe attacks.[4] Orthotopic liver transplantation is curative and can be resorted to in refractory cases.[5] In addition, recent advances in gene therapy show great promise in the treatment of this disease.

Learning Points

1. Acute Intermittent Porphyria is to be strongly suspected in the setting of recurrent neurovisceral symptoms.
2. Proper techniques of sample collection and testing such as preventing sample exposure to light, avoidance of time delay from collection to testing, are to be ensured to avoid false negative results.
3. The selection of antiepileptics to control seizure is to be done since many of the first line antiepileptics are precipitants of acute attacks.
4. Educate the patient on preventive measures and to discuss the disease with the treating doctor to avoid drugs and that may lead to precipitation of acute attacks.
5. Cortisol and ACTH deficiency is also described owing to underlying hypothalamic dysfunction and this can mislead to a diagnosis of adrenal insufficiency when presenting in the background of abdominal pain hyponatremia and hypotension. Steroids which are the mainstay of treatment for adrenal insufficiency can precipitate AIP.
6. Hyponatremia (due to vomiting /SIADH) is a frequent accompaniment and the altered sensorium may be attributed to it often missing the underlying diagnosis.
7. Acute Pancreatitis is well described in porphyria and can mislead the diagnosis.

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