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Episodic Hyponatremia in Acute Intermittent Porphyria: A Case Report

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Abstract

Background: Acute intermittent porphyria (AIP) is an uncommon, ubiquitously distributed autosomal dominant disorder with low penetrance characterized by decreased enzyme activity of hydroxymethylbilane synthase (HMBS) an enzyme of heme synthesis pathway. It is often an elusive diagnosis due to rarity and non-specific signs and symptoms. **Case report:** A 28 years old female from Nawalparasi (district in central Nepal) presented with history of recurrent episodes of abdominal pain and vomiting. Her current episode began two weeks before presentation to our center. Abdominal pain was diffuse, colicky in nature without exacerbating or relieving factor. There was no postural or diurnal variation. On examination, there was no tenderness and abdominal examination findings were unremarkable. Her biochemical investigations were unremarkable except for severe hyponatremia (S. Na of 100mmol/L) which was SIADH/SIADH like presentation (Table 1 and Table 2). Severe episodic hyponatremia, port-wine color of urine, gastrointestinal symptoms and previous hospital stay two years back with similar episode of hyponatremia and abdominal pain were valuable clues for suspicion of acute porphyria. On further evaluation, patient was found to have presence of porphyrogenic precursors in urine and diagnosis of acute intermittent porphyria was confirmed. After diagnosis, she was managed conservatively with carbohydrate loading with intravenous dextrose, opioids and pregabalin as analgesics. Her symptoms gradually improved, hyponatremia subsided and was discharged in normal condition. **Conclusion:** Acute intermittent porphyria has signs and symptoms common to several clinical, neurological, psychiatric and gastroenterological pathologies, which complicate diagnosis. In young patients with hyponatremia (with SIADH –like picture), AIP should be considered in differential diagnosis.

Key Words : Acute intermittent porphyria, Abdominal pain, Episodic Hyponatremia

Introduction

Symptomatic hyponatremia is a common presentation in emergency department. The frequency of hyponatremia depends on the definition used, clinical setting, and population studied, but is generally reported to affect 15% to 30% of acutely hospitalized patients.[1] Though the guidelines on management are well known, evaluation of hyponatremia is often very demanding and perplexing especially in resource-limited settings like Nepal. In this case report, we describe a case of 28 years old female with episodic hyponatremia and abdominal pain who on systematic evaluation of hyponatremia was diagnosed as acute intermittent porphyria.

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Case description

Twenty-eight-year-old female presented with complaints of pain abdomen for 15 days and vomiting for 10 days. Abdominal pain was diffuse, burning type of pain, with episodic colicky pain in between. It was non-radiating without any aggravating and relieving factors. She also had vomiting [3-4] episodes per day for

10 days, containing ingested food particle, non-blood mixed and non-bilious. She also complained of constipation with passage of hard stools every 5-7 days. There was no history of fever, jaundice, altered sensorium or blood in stool.

She was admitted in another center and was evaluated with blood investigations (Complete blood count, liver function tests, kidney function test, and inflammatory markers) as listed in Table 1. Reports were unremarkable except for isolated hyponatremia of 110 mmol/L which was first considered to be secondary to GI loss of electrolytes following vomiting. This had been managed with intravenous 3% normal saline initially, then with normal saline and salt capsules. Over her week-long admission, she persisted to have hyponatremia despite treatment. Endoscopy, CECT abdomen, colonoscopy and colonoscopic biopsy were also done for evaluation of her abdominal pain. These revealed antral gastritis and non-specific ileitis. CECT abdomen and pelvis showed distended ascending colon loaded with fecal matter with gaseous distension. Acute pancreatitis had been ruled out with normal serum amylase, lipase levels and imaging.

At this point she was referred to our center for endocrinology evaluation of her presentation.

At presentation to emergency department of our hospital, she complained of persistent pain in abdomen and was having colicky pain every 5-10 minutes. On examination, she was afebrile with pulse rate of 98 beats per minute, blood pressure of 110/60 mm of Hg and oxygen saturation of 98% on room air. There was no postural hypotension. Abdomen was soft and non-tender despite the diffuse pain, with no organomegaly. Chest and CVS findings were within normal limits. Her sensorium was normal (GCS: E4 V5 M6) with normal orientation to time, place and person. Her Sodium level came out to be 100 mmol/L. Spot urinary sodium was 41 mmol/L and urinary osmolality (calculated) was 110 mosm/kg at serum sodium of 100 mmol/L and serum osmolality of 210 msom/kg suggestive of SIADH or SIADH like presentation (Adrenal insufficiency/ Hypothyroidism). She was initially treated with injection of 3% normal saline, pantoprazole and hyoscine butyl bromide for her abdominal pain. Meanwhile, on evaluation of her SIADH / SIADH like causes of hyponatremia, there was no history or examination findings to suggest intra-cranial mass lesions, chest or abdominal mass/ infection. ESR was 17 mm/hr (done by Westergren method) and CRP was 11.28 (reference range 0-5) which practically ruled out infectious cause of SIADH. Plasma ACTH level, serum cortisol levels and TFT were sent for evaluation of SIADH like presentation. Serum cortisol of 11.80 microgram/dL (4.22-22.4) and ACTH level was 5.46 picogram/ml (Reference range: 7.2- 63.3). These tests were drawn at 5 pm to rule out adrenal insufficiency as patient had to be urgently evaluated at presentation, AI being an emergency. Thyroid function test was done which showed isolated high fT4 levels with fT3 and TSH within normal range: fT3: 4.2 pg/ml (2.3 -4.2), fT4: 2.38 ng/dL (0.89-1.76) and TSH:2.27 microIU/ml (0.35-5.5) done on ROCHE-COBAS platform which was unexplained at that point.

On reviewing her history, she had similar episodes of abdominal pain and hyponatremia requiring admission two years back with normal sodium levels in between without the need for water restriction or any medication/ therapeutic salt use. Even in this episode the patient could predict that the sodium levels would improve on its own from the then current value of 120 mmol/l which came as a surprise statement to us coming from a patient in hyponatremia. This provided us an

important clue of the hyponatremia event being episodic and following a predictable course for the patient. At this point, we narrowed our differential diagnoses to causes of intermittent hyponatremia with SIADH with normal ESR and minimally raised CRP. When asked specifically if she had passage of red colored urine, she admitted to having such grossly red urine during episodes of abdominal pain. This clenched the diagnosis as AIP clinically. On further probing, she revealed that the previous episode of hyponatremia was preceded by use of some mass immunization oral drug in her community (possibly Diethyl carbamazepine use for filariasis). Current episode though did not have any apparent trigger including history of recent fasting, alcohol intake, any implicated drug use. Her reports of hyponatremia from previous and current episodes have been shown in Table 2.

There is history to suggest excessive worrying even during periods of wellness and history of insomnia with tingling and numbness of limbs during the episodes. She was diagnosed as anxiety due to general medical condition and advised escitalopram for the same. On neurological examination, there was no evidence of objective sensory or motor neuropathy after her sodium levels were normal. NCV was not done due to unavailability.

There is no similar illness in the family and her family tree is presented in Figure 1.

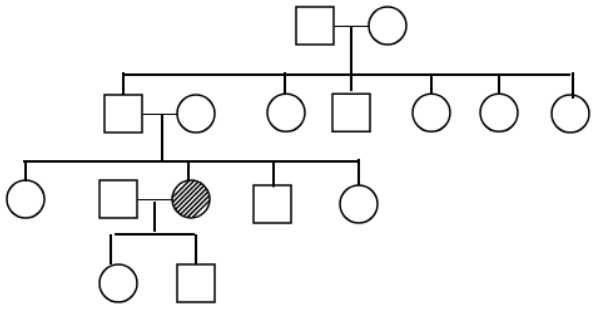

Figure 1 Family tree of the patient.

She had persistent pain abdomen which was managed with injection tramadol. Serum sodium level increased from 100 mEq/L to 118 mEq/L with use of hypertonic saline followed by salt capsules with water restriction over 2 days. After the clinical diagnosis of AIP, she was given high carbohydrate diet with iv dextrose infusion. Urine for porphyrin precursors were soon dispatched to a reference lab in New Delhi. Her pain symptoms gradually improved and she was discharged on persistent request at 20 percent of her initial pain intensity in 24 hours of dextrose use.

At follow up at one week, her urine porphyrin precursors report came out to be positive (method Column chromatography). Her urine sample at that visit was port wine red (Figure 2A and 2B). Further confirmatory tests of 24-hour urinary porphyrins could not be sent due to financial constraints. Patient was still considered a confirmed case given the absence of history to suggest lead toxicity (absence of basophilic stippling of RBCs on peripheral smears, lack of signs of motor neuropathy) which is considered a cause of falsely elevated urine porphyrins.

Patient has had three months of follow up since then and has no abdominal pain or hyponatremia. Escitalopram has been continued. She has been adequately counselled for avoiding porphyrogenic precipitants like stress, alcohol, low carbohydrate diet and

implicated drugs and for maintaining periodic follow up. Liver elastography (FibroscanTM) was done which showed a normal LSM value of 4.8 kPa ruling out occult fibrosis. She has also been planned for periodic ultrasound of the liver to pick any early Hepatocellular carcinoma which uncommonly happens even without cirrhosis in AIP.

Figure 2 B: Port wine color urine in plastic container

Figure 2A : Port-wine color urine in plastic container

Table 1: Lab parameters

	Test	Results	Normal range/Unit
Hematology			
	Haemoglobin	10.3	11-17 g/dl
	Platelets	216000	150000-400000 / mm^3
	Total leucocyte count	8500	4000-11000 / mm^3
	Differential count		
	Neutrophil	67	40-70%
	Lymphocyte	25	25-45%
	Eosinophil	00	2-6%
	Monocyte	08	2-10%
	Basophil	00	0-1 %

Renal Function tests			
	Urea	31	15-45 mg/dl
	Creatinine	0.7	0.5-1.4 mg/dl
Liver function tests			
	Bilirubin total	1.18	0.2-1 mg/dl
	Bilirubin direct	0.53	0.1 – 0.4 mg/dl
	SGPT/ALT	49.27	<45 IU/L
	SGOT/AST	60.6	<40 IU/L
	Alkaline Phosphate	65.49	50-136 U/L
	Total protein	6	6-8.2gm/dl
	Albumin	3.55	3.4-5.5 gm/dl
Thyroid function tests			
	Free T3	4.2	2.3-4.2 pg/ml
	Free T4	**2.38**	0.89-1.76 ng/dl
	TSH	1.47	0.35-5.6 microIU/ml
Others			
	ESR	17	mm/hr
	Calcium	7.64	8-11 mg/dL
	Phosphorus	2.78	2.8-5 mg/dl
	CRP	11.28	0-5 mg/L
	Adrenocorticotrophic hormone (ACTH)	5.46	7.2-63.3 pg/ml
	Cortisol	11.8	4.3-22.4 microgm/dl

Table 2: Serial monitoring of Sodium and Potassium

Date	Sodium (Range 135-145 mmol/L)	Potassium (Range 3.5-4.5 mmol/L)
2023/09/24	100	2.5
	101	2.5
	106	2.4
2023/09/25	108	2.6
	110	2.9
	113	3.6
	118	4.2
2023/09/26	119	3.4

2023/09/27	120	3.8
2023/09/27	122	3.6
2023/10/02	108	2.7
	118	3.43
2023/10/03	120	3.35
	125	4.35
	126	3.72
2023/10/04	122	4.4

Discussion

We have described a classic case of acute intermittent porphyria diagnosed based on consistent signs and symptoms i.e. abdominal pain in a young female presenting with hyponatremia. Much has been written on the epidemiology, pathophysiology and management of AIP which is a rare ubiquitously described metabolic disorder.[2] We shall discuss about reaching to the diagnosis from an endocrine perspective.

Endocrinologists are routinely consulted on cases with hyponatremia due to suspicion of adrenal insufficiency. Therefore, hyponatremia is our starting point in many of these cases. Hence, having a systematic approach to its evaluation is a must. The European society of endocrinology, in collaboration with experts from oncology, nephrology as well as intensivists came up with guidelines on evaluation and management of hyponatremia in 2014.[3] This evidence driven guidelines classifies causes of hyponatremia into euvolemic, hypervolemic or hypovolemic hyponatremia using urine sodium level which makes it more objective and discrete against the traditional classification based on history and clinical evaluation of blood volume.[3] Euvolemic hyponatremia comprises the most common category under hyponatremia. Further, SIADH due to various causes remains the most popular sub-classification under euvolemic hyponatremia. SIADH again has a non-exhaustive list of causes including drugs, infections, inflammation, malignancies, etc. It is often here where the diagnostic algorithms go mute and leaves it to best clinical evaluation.[3] Our case of AIP also fell in the same category of hyponatremia with SIADH.

Unlike the hyponatremia caused by vomiting in other causes of acute abdomen, urine sodium and osmolality remain high in SIADH of AIP. Therefore, evaluation with urine sodium and urine osmolality is important to consider AIP in the list of differential diagnoses.

Adrenal insufficiency is a common cause of hyponatremia with SIADH-like presentation.[4] Once glucocorticoids or mineralocorticoids have been started without baseline ACTH and cortisol level, these results and that of urine Na and urine osmolality become spurious. Reaching to a confirmatory diagnosis of adrenal insufficiency or any other cause of

hyponatremia becomes difficult thereafter. Fortunately, in our case, we sent ACTH level and cortisol level even at 5pm as the patient arrived around that time in the ER. Serum cortisol was 11ug/dl, which does not rule out adrenal insufficiency with the traditional cut offs (18ug/dl), but knowing diurnal variation of cortisol levels in serum helped us gauze at a higher morning cortisol level, which would effectively rule out adrenal insufficiency. Evening cortisol level have been shown to be half of morning cortisol levels in serum.[5] A Plasma ACTH level of 8pg/ml also ruled out primary adrenal insufficiency which is usually two times above the upper limit of normal in primary insufficiency.[6] We were left with evaluation in lines of neurological causes only after ESR, CRP came to be normal and mildly elevated respectively (rules out most infectious and inflammatory causes). This helped us think of acute intermittent porphyria as a differential. We also realized that among the causes of 'episodic' hyponatremia with SIADH as presentation, only a few cases have been described namely in MELAS syndrome and intermittent diuretic use.[3,7] The episodic nature of hyponatremia in acute intermittent porphyria has not been highlighted enough probably because of the neuro-visceral abdominal symptoms which receive bulk of the attention in case reports.[8] In our case, we had discretely established by history that patient had an episodic hyponatremia requiring no treatment in between which helped us think from a pathophysiological point of view of the etiology being a trigger dependent intermittent decompensation of a quiescent disease which is unlike how most infections and malignancies behave. The isolated high T4 levels in our case is explained by high thyroid binding globulin (TBG) that is known to be present in acute intermittent porphyria.[9]

Conclusion

Acute intermittent porphyria is a rare metabolic disorder of heme synthesis which presents with severe hyponatremia and abdominal pain which can be challenging in diagnosing the condition. A systematic approach to evaluation of hyponatremia, with considerations for its episodic nature can be helpful to reach the diagnosis.

Declarations

Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review on request.

Conflict of interests: No conflict of interests.
Funding: None
Data availability statement: All the clinical records of the patient are available for review by editor in chief upon reasonable request.

Author's Contribution:

Biraj Baral (BB), Samit Lamichhane (SL) were involved in the evidence collection and conceptualization of the study. SL and BB drafted the initial version of the manuscript. Saurav Khatiwada (SK), Barun Shrestha (BS) and Mukesh Kumar Ranjan (MKR) guided through whole process of conceptualization and finalization of manuscript. All the authors approve of the final version of the manuscript.

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