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Abstract

Objective
We present a case of acute intermittent porphyria with accompanying euvolemic hyponatremia from elevated ADH triggered by an implanted hormonal contraceptive device.

Case description
A 19-year-old African-American female with history of childbirth two months prior presented to the emergency department of Grady Memorial Hospital with vague but severe back pain and found with marked hyponatremia of 125mEq/L. Serum sodium level decreased to 113mEq/L after volume resuscitation with 0.9% sodium chloride. The patient experienced progressive decline in mental status and a generalised tonic clonic seizure. Patient was admitted to intensive care unit and improved with administration of 3% sodium chloride. Extensive evaluation for etiology of euvolemic hyponatremia was initially unremarkable, and patient was managed with free water restriction, hypertonic sodium chloride, vasopressin receptor antagonists, and antihypertensive medications. Empiric removal of a recently inserted etonogestrel implant was performed with resolution of patient’s symptoms. Approximately 2 weeks following hospital discharge, the send-out lab for urine porphobilinogen was found to be notably elevated.

Introduction
Acute Intermittent Porphyria (AIP) is one of several disorders that arise from enzymatic derangements in the biosynthetic pathway of the heme molecule. AIP is the most common of the acute porphyrrias worldwide, with an estimated prevalence of approximately 5 per 100,000 people [1]. Specifically, AIP results from a defective copy in one of the two genes for Porphobilinogen (PBG) deaminase, leading to the inadequate synthesis of the normal enzyme. Typically, patients will be symptom-free until a precipitating factor causes increased transit through the porphyrin metabolic pathway, resulting in accumulation in Aminolevulinic Acid (ALA) and Porphobilinogen (PBG) (Figure 1) [2-4]. AIP is the second most common porphyria but can have variable expression making diagnosis difficult [5]. We describe a case of acute intermittent porphyria that presented with non-specific lower back pain and progressive acute hyponatremia complicated by seizure, acute enceephalopathy, tachycardia, and hypertension.

Case Description
A 19 year old African-American recently post-partum female with no known past medical history presented to the emergency department of Grady Memorial Hospital for a 3 day history of worsening mid-back pain and fatigue. Two months prior to admission, the primigravida delivered a pre-term infant at 27 weeks gestational age following spontaneous rupture of membranes. At that time, she received antenatal steroids, tocolysis, empiric group B Streptococcus prophylaxis, and had an uneventful vaginal delivery. She was discharged two days after delivery. There is no mention of eclampsia or preeclampsia during review of outside records.

She recovered well and elected to have an etonogestrel 68 mg implant (Implanon®, Merck & Co., Inc., Whitehouse Station, NJ, USA) placed in her left arm for contraception, which was performed two weeks prior to this presentation. The patient continued to produce and pump breast milk throughout this time. The day prior to admission, she presented to an Emergency Department (ED) at another hospital for mid-back pain and fatigue, was diagnosed with a viral syndrome, and was discharged with pain medication. Two days after discharge, her pain persisted and she was subsequently transferred to our facility.

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and discharged home. Notable laboratory studies from that visit revealed sodium of 131mEq/L and creatinine of 1.26mg/dl (baseline 0.7-0.8). The following morning the patient continued to experience severe back pain. The patient's parents noticed worsened fatigue, prompting presentation to our ED for further evaluation. On the day of admission, the patient also described three days of decreased appetite and nausea.

Initial physical examination was unremarkable; the patient's back was not tender to palpation, nor could pain be elicited by musculoskeletal or costovertebral angle maneuvers. Laboratory evaluation revealed a sodium level of 125mEq/L and a creatinine of 1.1mg/dL. Initial imaging, including CT renal stone protocol and CT Head without contrast, was unrevealing. The ED physicians assessed the patient as having hypovolemic hyponatremia, and administered a two liter bolus of 0.9% sodium chloride (NaCl). Following this, the patient's mental status deteriorated and repeats sodium was decreased to 116mEq/L, prompting consultation to the Medical Intensive Care Unit (MICU) service for progressively symptomatic and worsening acute hyponatremia. On MICU evaluation, repeat physical examination suggested patient was currently at or near euvoemia. On neurological exam, she was now obtunded and unresponsive to verbal or painful stimuli with a disconjugate gaze and absent patellar reflexes. Sinus tachycardia to 120s and marked hypertension with systolic blood pressures in the 200s were noted. She was admitted to the MICU for intensive monitoring of sodium and acute treatment of hyponatremia and hypertension. While en route to ICU, she suffered a witnessed general tonic clonic seizure of two minutes duration prompting emergent intubation for airway protection.

Immediate laboratory data post-seizure revealed sodium level of 113mEq/L. Urine sodium of 174mEq/L, urine osmolality of 473mOsm/kg, and serum osmolality of 245mOsm/kg. Sinus tachycardia to 120s and marked hypertension with systolic blood pressures in the 200s were noted. She was admitted to the MICU for intensive monitoring of sodium and acute treatment of hyponatremia and hypertension. While en route to ICU, she suffered a witnessed general tonic clonic seizure of two minutes duration prompting emergent intubation for airway protection.

<table>
<thead>
<tr>
<th>Etiologies of SIADH</th>
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<td>Other causes of excessive ADH</td>
<td>Normal TSH and cosyntropin stimulation test</td>
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<td>Hypothyroidism</td>
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<td>Malignancy</td>
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<td>Gastrointestinal Lymphoma</td>
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<td>Genitourinary</td>
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| Infection | Negative chest CT, absence of clinical symp-
mptoms consistent with infection |
| Tuberculosis |  |
| Pneumonia |  |
| HIV | Negative HIV testing during pregnancy per OSH records and Negative HIV testing during current hospitalization |
| Intracranial processes |  |
| Brain tumors |  |
| Traumatic brain injury |  |
| Encephalitis |  |
| Multiple sclerosis |  |
| Sheehan’s syndrome |  |
| Medications/Ingestions | Was not on any of these medications at presentation |
| SS RiS |  |
| Narcotics |  |
| Antipsychotics | Drug/volatile screen negative, with exception of elevated acetone level from starvation ketosis |
| NSAIDs |  |
| Ecstasy |  |
| Others |  |
| Acute Intermittent Porphyria (AIP) | Elevated urine porphobilinogen - result available after hospital discharge |
| Acute psychosis | Psychiatric consultation did not suggest postpartum psychosis |

Table 1: Relevant differential diagnosis of SIADH and corresponding diagnostic work-up for our patient’s presentation.

and hypertension also improved, permitting discontinuation of opiate pain medications and oral anti-hypertensives; however, she continued to have persistent, asymptomatic tachycardia. The patient’s appetite returned, with unusual cravings for high carbohydrate containing foods. She was discharged on hospital day 13 and was seen in clinic two weeks later with a sodium level of 138 and resolved tachycardia.

Approximately 5 days after hospital discharge, the physician was notified of an elevated urine porphobilinogen (a send-out lab that normally takes 2-3 weeks to result) of 56.80mg/g creatinine (Reference Range < 2.0mg/g creatinine). Patient was informed of this finding and follow up with Benign Hematology Clinic was arranged. She was not on any of these medications at presentation.

Discussion

Acute intermittent porphyria can be a diagnostic challenge, as it presents with a constellation of nonspecific but oftentimes severe symptoms such as abdominal or back pain, autonomic dysfunction manifested as hypertension and tachycardia, and progressive muscle weakness and neuropathy [8,9]. Severe AIP crises can rapidly progress to encephalopathy often secondary to hyponatremia from an elevated ADH state, respiratory failure from diaphragm paralysis, and psychosis with marked agitation [10,11]. It should be noted that, in the acute presentation, it can be difficult to clinically distinguish...
appropriate ADH release from volume depletion from inappropriate ADH release (SIADH) in these cases as many patients have acute volume depletion at presentation, and it is known that patients with porphyria have a lower blood volume at baseline [12]. On the basis of the MICU team physical exam suggesting euolemic state and 2L fluid bolus with 0.9% NaCl by the ED, our team interpreted the urinary studies to be consistent with an SIADH state while admitting that this may not be entirely the case. In addition to encephalopathy, other important diagnostic clues for AIP include dark reddish-brown urine on pH testing and elevated spot urinary porphobilinogen, usually indicative of an acute symptomatic attack. Low porphobilinogen deaminase activity can be detected during times of disease remission [13]. The mainstay of AIP management involves the avoidance of suspected precipitants [14]. Well-known precipitants include sulfonamide antibiotics, anti-epileptics, Oral Contraceptive Pills (OCPs), alcohol, decreased caloric intake, stress, and smoking [15]. In addition to symptomatic management, glucose or intravenous heme (heme arginate in Europe or panhematin in the USA) can be administered to reduce starvation ketosis and ALA synthesis, respectively, in those patients with known or highly suspected cases of AIP [8,9,14].

Six weeks after a recent childbirth, our patient elected to have an etonogestrel implant inserted into her arm as a contraceptive method. Two weeks later, the patient experienced symptoms and laboratory findings consistent with AIP. In review of porphyrinogenic medications listed on the Porphyria Foundation’s drug database, progestins are listed as unsafe due to their ability to induce accumulation of porphyrins [16]. We believe that the progestin-only contraception, in addition to her recent decreased caloric intake, triggered this AIP crisis and, ultimately, established the patient as suffering from porphyria. Following removal of etonogestrel implant and discontinuation of other porphyrinogenic medications (such as nicardipine), the patient’s clinical status, including symptomatic symptoms, dramatically improved. Despite studies demonstrating the association of AIP attacks with oral contraception [17,18], importantly and to our knowledge, none have reported the role of an implanted contraceptive in precipitating overt AIP. Adding to the unusual nature of our patient’s case is the rarity of AIP among African and African American populations. A review published in 2000 noted that only 38 patients have been reported with AIP and African ancestry, and this is thought to be due to a different spectrum of mutations in the Porphobilinogen Deaminase gene (PBGD) in the African population compared to the Caucasian population [19,20].

Sex hormones such as estrogen and progesterone have been previously implicated in the precipitation of acute AIP crises [15,21-23]. Approximately 10-30% of women with porphyria experience cyclical AIP attacks, an association thought to be secondary to progestosterone’s induction of ALA synthase, one of the major rate-limiting steps in heme synthesis [18]. This relationship of AIP with progesterone is further established by improved clinical symptoms with the use of Gonadotropin-Releasing Hormone (GnRH) agonists in patients with recurrent cyclical AIP attacks [21]. GnRH agonists decrease the number of pituitary GnRH receptors, leading to suppressed hypothalamic-pituitary-ovarian axis and decreased progesterone release [18]. Furthermore, in a Swedish population-based study, questionnaires administered to 166 women with clinical or latent AIP demonstrated that 24% of participants experienced an AIP attack with concurrent OCP use, and 18% of respondents stated that OCPs actually precipitated their first AIP attack [17]. AIP attacks can also occur during pregnancy but first presentations of AIP are rare during this time. A single case series, by Keung et al., described women with latent or undiagnosed AIP presenting with overt clinical symptoms during pregnancy or postpartum period. However, it is unclear whether the hormonal changes occurring during pregnancy alone are sufficient to exacerbate AIP, as most women described in this case series also experienced the use of a potential aggravating medication, comorbid infections, or decreased caloric intake [24].

Once the precipitating medications were removed, our patient required symptomatic treatment alone without the use of heme. Interestingly, our patient’s family did note an uncharacteristic high-carbohydrate diet. These cravings could illustrate the role of carbohydrate loading in the suppression of ALA synthase and subsequent decreased production of intermediate porphyrins. Although high carbohydrate diets have previously been advocated as integral to preventing future AIP attacks, and were commonly used in the treatment of AIP prior to heme availability, the benefit of high carbohydrate diets has not been scientifically proven [25].

Once the diagnosis of AIP is suspected and/or confirmed in a patient, it is advisable to refer the patient to one of the participating clinical centers in the Porphyrias Consortium of the Rare Disease Clinical Research Network. There are nine such clinical centers located in the USA. In addition, patients should be informed of the availability of genetic testing through the Department of Genetics & Genomic Sciences at the Icahn School of Medicine at Mount Sinai in New York, New York [26].

Conclusion
Acute intermittent porphyria requires high clinical suspicion, especially in young females with abdominal pain out of proportion to physical exam, SIADH, and new-onset hypertension. Because of the low prevalence of this disease in the United States, AIP was, admittedly, not high on our initial differential diagnosis for our patient’s presenting signs and symptoms. However, a negative history and laboratory work-up for eclampsia, Sheehan’s syndrome, intoxication, and adrenal insufficiency prompted reconsideration of more rare diagnoses. An elevated spot urine porphobilinogen, review of the patient’s recent medications, and the collection of clinical symptoms in a relatively healthy 19 year old female suggested an acute exacerbation of undiagnosed latent AIP. Our particular case demonstrated newly diagnosed AIP with acute attack likely prompted by recent etonogestrel implant insertion and complicated by decreased nutritional intake. The importance of recognition and diagnosis is paramount to preventing morbidity and life-threatening consequences of AIP, and AIP should be considered as a rare cause of euolemic hyponatremia in critically ill patients.

References


23. Rare Disease Clinical Research Network. The Porphyrias Consortium.