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Case Report

Paediatric hereditary coproporphyria: a diagnostic challenge

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ABSTRACT

Hereditary coproporphyria (HCP) is a hepatic porphyria, presenting with acute attacks of neurovisceral symptoms. We present a case of a young girl presenting with abdominal pain and vomiting episodes starting with menses. She also had severe hyponatremia and seizures. Laboratory investigations including urine and fecal protoporphyrin were negative, 10% dextrose solution and sodium level correction with supportive treatment was given. With this treatment her condition significantly improved but she presented again after a month with similar complaints at the time of her menses. Genetic testing was done and diagnosis of HCP was made. It can be concluded that considering Porphyrias in the differential diagnosis for repeat episodes of unexplained abdominal pain can help initiate early treatment and prevent complications.

Keywords: HCP, Abdominal pain, Neurovisceral, Young age

INTRODUCTION

Hereditary coproporphyria (HCP) is a rare autosomal dominant condition with variable penetrance resulting from genetic defects in the coproporphyrinogen oxidase, an enzyme in heme synthesis pathway. HCP manifests due to the accumulation of toxic porphyrin precursors, particularly coproporphyrin III, predominantly in the liver, and exhibits a wide spectrum of neurovisceral manifestations. The most common symptom of acute HCP is severe abdominal pain with nausea and vomiting. The other common clinical features include seizures, motor neuropathy, tachycardia, hypertension and constipation.[1] In some cases, it may be accompanied by photo-sensitivity with skin lesions.[2] Treatment usually involves intravenous glucose and hemin therapy.

CASE REPORT

A 14 years-old girl presented to the emergency department (ED) with history of diffuse abdominal pain since 2-3 days that worsened over the past 24 hours accompanied by multiple episodes of vomiting. She had her menses on previous day of admission.

On examination she was conscious and oriented to time, place and person. She was febrile and dehydrated; Icterus was present. Patient was restless. Vital parameters were as follows, respiratory rate of 30 breaths/min, a heart rate of 122 beats/min, initial BPre 150/90 mmHg and oxygen saturation was 95% on room air. On mental status examination, the patient was awake and alert. Abdominal Examination revealed mild tenderness on deep palpation, mainly in the epigastric area and no abdominal mass. Bowel sounds were normal.

In ED, labs showed low heamoglobin conc. 10.3 gm/dl with reduced MCV (69.6 fL), TLC 11,030/mm^3 and platelet count 2,01,000/mm^3. Serum sodium level was lower than normal, measuring 113 mEq/L. Rest of routine biochemical panel within reference limits for potassium, calcium, magnesium, phosphorus, urea and creatinine. Liver function tests showed normal serum proteins, SGOT, SGPT and alkaline phosphatase with raised serum bilirubin levels (3.57 mg/dl). Routine urinalysis revealed presence of plenty of RBCs, indicating hematuria and microalbuminuria.

Immediately intravenous line was secured and IV fluids were started. She was then investigated for causes of jaundice and hyponatremia and treated with supportive care including IV antibiotics and sodium replacement.

During the course of treatment, she had an episode of generalized tonic-clonic seizures on day 2. Anti-epileptics were started. CT brain was done, which was normal. She was shifted to intensive care unit for further management.

She had another episode of convulsions on day 3 of admission. She became disoriented and irritable. Her clinical condition did not improve and even worsened. She needed to be intubated due to her low GCS and central line insertion was done.

Given presentation, several potential differential diagnoses were considered, including acute porphyria, urinary tract infection, renal calculi, gastrointestinal pathology, Wilson's disease, meningoencephalitis, and autoimmune conditions.

Further investigations were done to narrow down our differentials and the reports were as follows: CSF, blood, and urine cultures were sterile. Viral work-up for Herpes simplex virus (HSV) and COVID tests were negative. Various autoantibody tests including ANA, c-ANCA, p-ANCA, ASMA, AMA, Anti-LKM came back negative. Serum inflammatory markers (C-Reactive protein and D-dimer) were within normal limits. Urinary copper level and ceruloplasmin levels were normal. No Kayser-Fleischer rings seen. Urine porphobilinogen, a marker for acute porphyria, was also negative.

Abdominal USG revealed presence of echogenic sludge in gallbladder lumen, but no other significant findings were observed. Brain imaging with MRI showed mild diffuse cerebral and cerebellar edema along with thrombosis/ decreased blood flow in right middle cerebral artery branches, loss of flow void in left sigmoid sinus.

Her Na levels kept fluctuating throughout hospitalization.

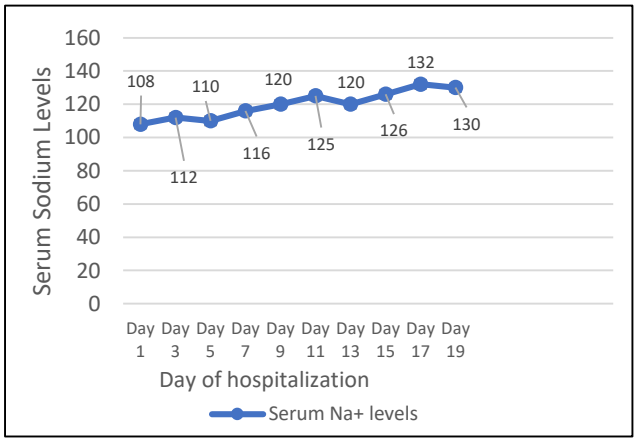
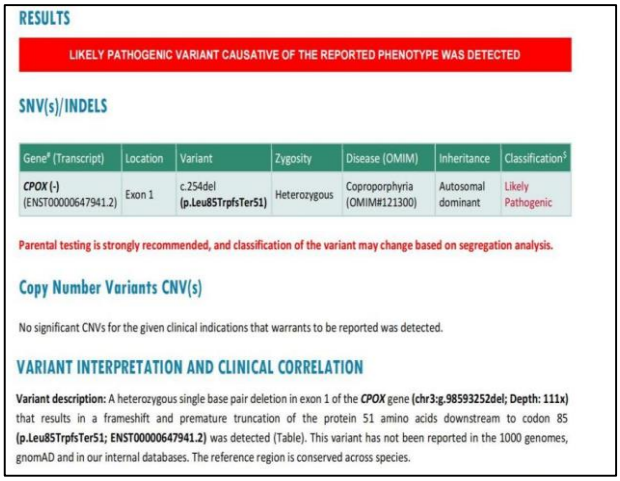


Figure 1: Serum sodium level fluctuation throughout hospitalization.

She was managed conservatively by 10% dextrose infusion and oral sodium bicarbonate tablets (300 mg). Nausea was managed with ondansetron. Lactulose solution and ursodeoxycholic acid were also added to the regimen. Finally, gradual improvement was observed and she was managed conservatively with supportive care, with her final diagnosis still being doubtful. She was discharged after 20 days of hospital stay and her general condition was stable.

The patient presented with similar symptoms a month later, coinciding with the time of her menstrual cycle. Her time of onset of symptoms, repeat abdominal pain, hyponatremia and seizures raised a high suspicion of acute porphyria as a possible underlying cause. According to American porphyria foundation, the first-line screening test is a measurement of urinary porphobilinogen (PBG) during the acute attack. Her urine PBG was normal (0.1 mg/L; normal range 0.0-2.0 mg/L). Fecal coproporphyrin levels were also not elevated. Consequently, she was referred for genetic testing, which revealed a heterozygous mutation (c.254del) in the CPOX gene, confirming the diagnosis of HCP.



RESULTS

LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

SNV(s)/INDELS

Gene[a] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[2]
CPOX (-) (ENST00000647941.2)	Exon 1	c.254del (p.Leu85TrpfsTer51)	Heterozygous	Coproporphyria (OMIM#121300)	Autosomal dominant	Likely Pathogenic

Parental testing is strongly recommended, and classification of the variant may change based on segregation analysis.

Copy Number Variants CNV(s)

No significant CNVs for the given clinical indications that warrants to be reported was detected.

VARIANT INTERPRETATION AND CLINICAL CORRELATION

Variant description: A heterozygous single base pair deletion in exon 1 of the *CPOX* gene **(chr3:g.98593252del; Depth: 111x)** that results in a frameshift and premature truncation of the protein 51 amino acids downstream to codon 85 **(p.Leu85TrpfsTer51; ENST00000647941.2)** was detected (Table). This variant has not been reported in the 1000 genomes, gnomAD and in our internal databases. The reference region is conserved across species.

Figure 2: Genetic testing report showing presence of pathogenic variant of CPOX gene.

She was similarly treated with 10% dextrose along with hyponatremia correction and supportive care. She recovered with this treatment and was discharged after 10 days of hospital stay.

After her recovery, she was discharged and instructed to avoid sun exposure and porphyrinogenic medications. Genetic testing of the family for porphyria was advised, and outpatient follow- up has been arranged.

DISCUSSION

Porphyrias is a group of diseases, characterized by defect in one of the eight enzymes mediating the pathway of heme synthesis. They are generally classified into two groups: the hepatic and erythropoietic types. In hepatic

forms the excess porphyrins and its precursors originate from liver and in erythropoietic forms it originates from the bone marrow. Clinically they are classified as "acute porphyria" if they are characterized by sudden attacks of pain and neurologic symptoms.

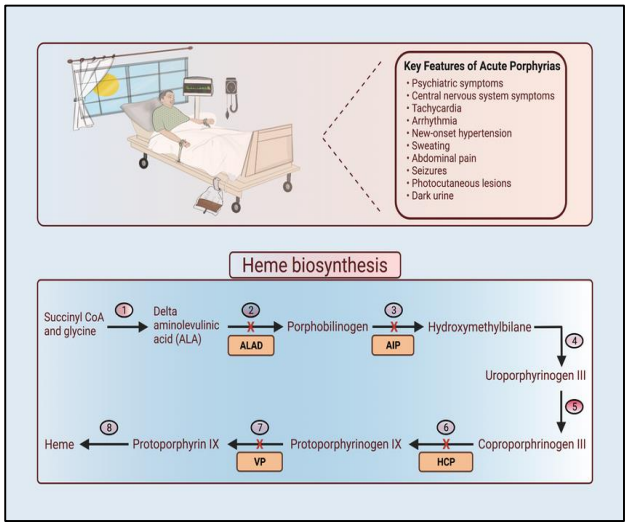


Figure 3: Pathway of heme biosynthesis. The eight steps of heme synthesis are shown below, and each number represents the enzyme that catalyzes each step. Defects in steps 2, 3, 6, and 7 cause acute porphyria; step 2 representing ALA dehydratase and its deficiency porphyria, step 3 representing porphobilinogen deaminase and its deficiency of acute intermittent porphyria, step 6 representing coproporphyrinogen oxidase and its deficiency of HCP, and step 7 representing protoporphyrinogen oxidase and its deficiency of variegate porphyria.
This figure is created with BioRender.com.[3]

HCP is a rare acute hepatic porphyria with an estimated incidence of 2 active cases per 1,000,000 people.[4] It was first described in 1955 by Berger and Goldberg.[5] HCP is an autosomal dominant variant of acute porphyria which results from the deficiency of coproporphyrinogen III oxidase enzyme. The gene encoding this enzyme is located at 3q12.[6] This deficiency leads to dysfunctional heme biosynthesis, causing increased levels of heme intermediates such as delta- aminolevulinic acid (ALA) and porphobilinogen (PBG). Accumulation of ALA and PBG, is believed to be the primary cause of the disease manifestations.

The most common clinical manifestations are abdominal pain (89%), followed by neurologic (33%), psychiatric (28%), cardiovascular (25%), and skin symptoms (14%).[7] In between attacks, it is often asymptomatic. A variety of triggers can lead to acute attacks in susceptible individuals, including hormonal fluctuations in women, infections, stress, use of certain medications (most commonly barbiturates, estrogens, sulfonamides, and hormonal oral contraceptives), alcohol and fasting/low-calorie diets. The attacks usually begin by the age of 20-30 years or sometimes at the onset of puberty. They are more common in females.[4]

Symptoms are unusual before puberty and vary greatly in the phenotypic expression. Acute attacks usually consist of colicky abdominal pain with constipation, vomiting, and fever. They typically last days to weeks and recur intermittently. Psychiatric mood symptoms can also accompany or precede the abdominal attacks. Associated peripheral polyneuropathy usually presents with back and leg pain with cramps, severe cases can progress to a flaccid quadriparesis with respiratory failure. Some patients may present with seizures which may be partial or generalized or even as status epilepticus. The exact etiology is unknown but it may relate to γ-aminobutyric acid (GABA) receptor binding by δ-aminolevulinic acid. In addition, defects in hepatic heme synthesis can alter brain levels of neurotransmitter substrates, such as tryptophan, which may be important.[8] The seizures during acute attacks may also be due to fluid and electrolyte imbalance (most commonly hyponatremia). Imbalance may be caused by excessive vomiting and inappropriate antidiuretic hormone secretion.[9]

The initial screening test performed is urinary porphobilinogen (PBG), aminolevulinic acid (ALA), and porphyrins.[4] They are usually raised during an acute attack but may be normal in between attacks. These tests can be performed on a random (spot) urine sample that should be protected from light after collection and during transport to the laboratory. If urinary PBG excretion is increased, then further testing (fecal and blood porphyrin measurement) is necessary to distinguish HCP from variegate porphyria. The fecal coproporphyrin (predominantly isomer III) levels are very useful as they are raised in HCP.[10] Screening tests should be confirmed genetic testing for detection of pathogenic variant for CPOX gene is the confirmatory test.[11]

Treatment of acute attacks includes intravenous carbohydrate, usually as a 10% dextrose solution and infusions of hematin or heme-arginate, if glucose therapy is inadequate. Hematin is used to halt acute attacks by preventing the further formation of toxic porphyrin intermediates. Hospitalization is often necessary for acute attacks. Medications for pain, nausea, and vomiting and close observation are generally required. The associated metabolic abnormalities such as hyponatremia and water imbalance should also corrected. The trigger of the attack must be noted and treated accordingly. Premenstrual attacks can be managed by ovulation suppression with gonadotropin releasing hormone analogues. If low calorie intake is the cause, dietary counselling is needed. The drugs which may precipitate an attack should be avoided and sun exposure should be reduced.

It should be emphasized that our patient has exhibited an unusually early age of onset for HCP, as pediatric presentations of heterozygous HCP are rare. The exact reason of her urine PBG and fecal COPRO III levels

being normal remains unclear. It may be due to sampling error or a variant of HCP, where the levels of PBG rapidly return to normal after an acute attack. Exacerbation with hormonal imbalance is documented and our patient presented with perimenstrual exacerbations. Two consecutive attacks coincided with her cycles which is a rare phenomenon. She was managed with conservative treatment with dextrose and she responded well. Hemin was not needed in our patient. This case highlights the importance of relying on clinical features as the laboratory investigations may not always come positive. But strong clinical suspicion and treatment based on it may lead to patient benefit. This case tells us the importance of pursuing genetic testing for prompt diagnosis and management in case the laboratory findings do not align with the expectations.

CONCLUSION

The diagnosis of HCP is challenging due to its varying clinical presentation and overlap of symptoms with other common diseases. An early diagnosis of HCP is required to prevent further attacks leading to permanent neurological damage or even death. So, it should always be considered in the differential diagnosis for unexplained abdominal pain in individuals presenting with accompanying symptoms of nausea, vomiting, constipation, pain in other parts of body, mental confusion, change in urine color, hyponatremia, tachycardia, and hypertension.

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