Case Report

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Porphyria: Psychiatric Sequelae or Comorbid Primary Psychosis?

T Patrick Jensen*

Medical Director, Covenant Health Psychiatric Consult and Liaison Service, USA

***Corresponding author:** T Patrick Jensen, Medical Director, Covenant Health Psychiatric Consult and Liaison Service, USA

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SUMMARY

40-year-old female with a history of psychotic disorder secondary to acute intermittent porphyria, intermittent explosive disorder, autism, and developmental delay who was admitted under observation for sepsis likely due to cellulitis. She has a history of psychosis either secondary to or exacerbated by acute intermittent porphyria episodes. This case highlights the diagnostic and management challenges of acute porphyria.

Learning Points:

a) Be able to identify primary vs. secondary psychiatric symptoms in the context of either dormant or acute exacerbation of porphyria.

b) Identify the common neuro-psychiatric complications of acute porphyria.

c) Be able to manage neuro-psychiatric symptoms of porphyria.

Background: Outline why this case is important and of interest to other clinicians in the field. Does it describe an unusual or novel occurrence, or a common health problem? The types of cases of interest include:

- Findings that shed new light on the possible pathogenesis of a disease or mechanism of therapy
- The case provides a somewhat novel complication of porphyria, that being exacerbation of a psychotic episode.
- This presentation of a rare disease is complicated by comorbid intellectual disability, attempts to discern primary vs secondary psychosis, and mood symptoms.
- It is challenging to diagnose primary vs. secondary psychosis and whether porphyria is dormant or acutely exacerbation.
- I discuss management of porphyria and complications.

Case Presentation

40-year-old female with a history of psychotic disorder secondary to acute intermittent porphyria, intermittent explosive disorder, autism, and developmental delay who was admitted under observation for sepsis likely due to cellulitis. The patient is alert and oriented to self only. She is an extremely poor historian. She denies depression, anxiety, suicidal ideation, homicidal ideation, and auditory and visual hallucinations. She does endorse paranoia, telling me that "she raped me and broke my leg." When I asked for specifics about these allegations, such as who did this, and when it occurred, she states "I do not know." When asked about a history of trauma including sexual and physical abuse, she tells me "My entire family are pedophiles." She denies there being any current abuse

but is unable to list any specifics regarding when these allegations occurred. She endorses nightly nightmares and flashbacks related to her reported history of abuse. She states she has been sleeping poorly, and when asked about her appetite, she states she is "learning." The patient's urine drug screen was negative. The rest of her substance use history is unknown. Past psychiatric diagnoses include psychotic disorder due to medical condition, autism, intermittent explosive disorder, and developmental delay. Previous documentation reports a history of a hospitalization during an exacerbation of acute intermittent porphyria. She is active with outpatient psychiatric services. Previous documentation reports past medication trials of Haldol, gabapentin, amitriptyline, Prozac, and Zyprexa. Medical history is remarkable for acute intermittent porphyria, anemia, cancer, dysphagia, GERD, glaucoma, Hodgkin's lymphoma, hypothyroidism, Port-A-Cath in place, thyroid carcinoma, cellulitis, chronic bronchitis, migraines, history of seizure disorder, sleep apnea, and Stickler syndrome. Documentation suggests that the patient lives with her mother who is her primary caretaker. The rest of her psychosocial history is unknown.

Physical Exam

- Patient is sitting up in bed eating her sandwich nondistressed, speech fluent, no facial droop
- Patient is alert, oriented times 0, cooperative, nondistressed
- Head is normocephalic, pupils round no scleral icterus
- Nares patent no discharge
- Oral mucosa moist no pharyngeal exudate or thrush
- Trachea is midline, no JVD, no accessory muscles of respiration usage
- Heart rate is regular, tachycardic
- Lungs clear auscultation, no rhonchi, crackles or wheeze
- Abdomen soft, nontender, nondistended, positive bowel sounds
- Extremities multiple hypopigmented areas on arms reminiscent of vitiligo. Erythematous ulcers right upper extremity.

Mental Status Exam

- Appearance.: Disheveled
- Behavior/Motor Activity: Normal
- Musculoskeletal: Observed muscle strength/tone within normal limits
- Gait/Station: Other: not observed
- Speech: Articulation difficulties, Impoverished
- Mood.: Good
- Affect: Constricted
- Thought Process/Associations: Perseverative, Other: Poverty of thought
- Thought Content.: Distorted, Delusional, Paranoid
- Cognition/Attention/Memory/Concentration: Disoriented, Inattentive during the interview and requires redirection
- Insight.: Impaired
- Judgement: Impaired
- Language: Within normal limits
- Fund of Knowledge: Adequate

Home Medications

- Acetaminophen (Tylenol Regular Strength 325 mg oral tablet), 650 mg= 2 tab, Oral, Q4H, PRN amitriptyline (amitriptyline 50 mg oral tablet) po QHS
- Famotidine(famotidine), 5 mg, Oral, Daily, PRN
- FLUoxetine (FLUoxetine 20 mg oral capsule), 20 mg= 1 cap, Oral, Daily
- Latanoprost ophthalmic (latanoprost 0.005% ophthalmic solution), 1 drop, Eye-Both, QPM
- Levothyroxine (Unithroid 175 mcg (0.175 mg) oral tablet), 175 mcg= 1 tab, Oral, Daily
- OLANZapine(OLANZapine 10 mg oral tablet), 10 mg= 1 tab, Oral, HS Table 1.

Table 1

Initial Labs:	
72 Hour Labs	
Event Name	Event Result
WBC	18.8 10x3/uL High
RBC	5.39 10x6/uL High
Hgb	14.8 g/dL
Hct	43.30%
MCV	80 fL Low
MCH	27 pg Low
MCHC	34 g/dL
RDW	16.2 % High
Platelets	308 10x3/uL
MPV	10.8 fL
Neutrophil % Auto	81.4 % High
Lymphocyte % Auto	10.7 % Low
Monocyte % Auto	7.30%
Eosinophil % Auto	0.30%
Basophil % Auto	0.30%
Absolute Neuts	15.3 10x3/uL High
Absolute Lymphs	2 10x3/uL
Absolute Monos	1.4 10x3/uL High
Absolute Eos	0.1 10x3/uL
Absolute Basos	0.1 10x3/uL
Sodium Lvl	136 mmol/L
Potassium Lvl	3.2 mmol/L Low
Chloride Lvl	91 mmol/L Low
CO2	29 mmol/L
Glucose Lvl	174 mg/dL High
BUN	11 mg/dL
Creatinine Lvl	0.77 mg/dL
Calcium Lvl	13 mg/dL Critical
Anion Gap	16 mmol/L High
eGFR AA	101 mL/min/1.73 m2
eGFR Non-AA	83
Lactic Acid Lvl	1.5 mmol/L
Lactic Acid Lvl	2.9 mmol/L Critical
Hemolysis	Not Detected CAP
Lipemia	Not Detected CAP
hs Troponin	12 ng/L
hs Troponin	15 ng/L High
hs Troponin Interpretation	AMI RULED OUT [3h]
hs Troponin Interpretation	INDETERMINATE [0h] Abnormal
hs Troponin Delta	3
hs Troponin Timeframe	200 min
Amphetamine Scrn Ur	Neg.
Barbiturate Scrn Ur	Neg.

Benzodiazepine Scrn Ur	Neg.
Cannabinoid Scrn Ur	Neg.
Cocaine Scrn Ur	Neg.
Methadone Scrn Ur	Neg.
Opiate Scrn Ur	Neg.
Oxycodone Scrn Ur	Neg.
Phencyclidine Scrn Ur	Neg.
Ethanol	<10.1
Ethanol Level	<0.01
UA Color	Yellow.
UA Appear	Turbid Iris Abnormal
UA Spec Grav	1.036 High
UA pH	6.5 pH Units
UA Protein	3+ Abnormal
UA Glucose	Negative Glu Iris
UA Ketones	1+ Abnormal
UA Bili	Neg.
UA Blood	3+ Abnormal
UA Nitrite	Neg.
UA Urobilinogen	Normal
UA Leuk Est	Neg.
UA RBC	>50 Abnormal
UA WBC	16-25 Abnormal
UA Squamous Epithelials	41-80 Abnormal
UA Bacteria	Trace.
UA Hyaline Cast	16-25 Abnormal
UA Mucous	Many. Abnormal
Influenza A	Neg.
Influenza B	Neg.
SARS-CoV-2 Antigen	Neg.

Initial Imaging

CT Brain/Head w/o Contrast.

Impression

No acute intracranial CT findings.

Individualized dose optimization technique was used for procedures performed.

XR Chest 1 View AP or PA.

EKG

Vent. rate 144 BPM

PR interval 126 ms

QRS duration 74 ms

QT/QTc 270/418 ms

P-R-T axes 21 13 53

Poor Data Quality, Interpretation May Be Adversely Affected, Sinus Tachycardiapoor R Wave Progression Cannot Rule Out Anterior Infarct, Age Undetermined, Abnormal Ecg, When Compared With Ecg Of 07-Aug-2018 15:02, Borderline Criteria For Anterior Infarct Are Now Present, T Wave Inversion Now Evident In Lateral Leads.

Follow-Up Examination 1

The patient was found to have cellulitis and hypercalcemia on initial exam. Cephazolin was initiated for cellulitis. Intact PTH, TSH and Vitamin D levels were obtained for hypercalcemia workup. The patient received fluid resuscitation. Zyprexa and Prozac were continued for treatment of psychosis and paranoid delusions. Amitriptyline was discontinued. PPG and ALA were obtained for acute intermittent porphyria workup.

Follow-Up Labs

Parathyroid Hormone Lvl = 16 pg/mL

TSH = 0.495 mcIntlUnit/mL

Vitamin D = 25 OH Lvl 5.14 ng/mL Low

B12 = 366 ng/mL

Unfortunately, the PBG and ALA were not obtained or sent out for unclear reasons.

Follow-Up Examination 2

Alert. Not answering questions directly or appropriately.

No cellulitic findings noted on exam today.

WBC 18 -> 6. Hemoconcentrated on arrival. Treated with IVF hydration.

Ca 13 -> 8.2. Hemoconcentrated on arrival. Treated with IVF hydration.

Follow-up Examination 3

The patient is a fair historian. However, she was disoriented to date, month, and year. She is not entirely oriented to her clinical situation. She does report having history of intellectual disability and special education. She does not know what her IQ is. She claims to be her own guardian. This is unconfirmed as I was unable to obtain collateral information. She reports that her mood is getting better. However, she does complain of migrainous headaches. She would not comment on whether she is experiencing photophobia or phonophobia. She does have a chronic history of headaches. She also reported that she had an unwitnessed seizure yesterday. She reported tremors that involved her entire body but she denies loss of consciousness. She does report having a diagnostic disorder of seizure disorder. She reports having followed by Neurology and reports history of Depakote therapy. Her liver function test is within normal limits. She does report a history of EEG. Her last EEG was normal. She did have elevated lactic acid upon admission for unknown causes, sepsis has been ruled out. She may benefit from repeating the lactic acid as she claims to have had a seizure yesterday. Her sleep is intact. Her energy, concentration, and appetite are intact. She continues to have violent ideations towards her mother. She does continue to have auditory hallucinations but denies command auditory hallucinations. She denies visual hallucinations. She complains of nausea as a side effect to her medications or as symptoms of porphyria.

The patient's Zyprexa was discontinued and Abilify 10 mg po qhs initiated as the patient complained of a longstanding side effect of nausea with Zyprexa. Prozac was decreased to 10 mg po daily, again to avoid potential ssri induced nausea. Depakote DR 250 mg po bid added given subjective reports of recent seizure activity and as a seizure disorder can be comorbid with acute intermittent porphyria.

Follow-Up Labs

Prolactin level is normal at 10.5 ng/mL.

Lactic acid level is normal at 1.5 ng/mL.

Follow-up Examination 4

The patient reports that she is feeling better. However, she does continue to have trauma related nightmares. She reports history of both physical and sexual abuse. She has nightmares, intrusive thoughts, and flashbacks as result. She also experiences avoidance behaviors and hypervigilance. She reports nightly nightmares interfere with sleep. We discussed prazosin therapy and she was amenable to treatment. The patient's energy and concentration are intact. Her appetite is poor and she states that this is secondary to porphyria. She denies any nausea. She denies suicidal ideations. However, she continues to have violent ideations towards her mother. She does not want to return back to the home. She also does not want to go into the psychiatric hospital but is under involuntary commitment at this time. The patient continues to have auditory and visual hallucinations but denies command auditory hallucinations. She denies side-affects to her medications. She is displeased with Prozac stating that she has been on this medication for at least a year without any efficacy. Of course, she is under dosed but because she has lost confidence we discussed a switch to Zoloft therapy and she was amenable to this. Abilify was titrated to 15 mg po qhs and Prozac discontinued with Zoloft initiated at 50 mg po daily. Prazosin 1 mg po qhs initiated for trauma related nightmares. The patient was accepted to a psychiatric hospital for further stabilization.

Investigation

Labs performed as above. EEG was not performed as there were no witnessed seizures or focal neurological deficits.

Treatment

The patient received antibiotic therapy for cellulites and IV fluid resuscitation for hemo-concentration. She received antipsychotic therapy for psychosis and ssri therapy for depression and PTSD.

Outcome and Follow-Up

This patient was followed as an inpatient for the course of five days until accepted to a psychiatric hospital.

Discussion

Acute intermittent porphyria (AIP) is caused by an inborn error of heme synthetic pathway. As such, there is an accumulation of neurotoxic heme intermediates or porphyins, particularly aminolevulinic acid (ALA) and porphobilogen (PBG) [1]. Although

ALA or PBG may be neurotoxic and perhaps responsible for the symptoms of the acute attack, this has never been established with certainty, and others have hypothesized that the acute attack may result indirectly from heme deficiency [2]. Though transmitted as an autosomal dominant inheritance pattern, the course of the illness is typically dormant with only 10% ever experiencing an acute porphyric episode [3]. AIP often presents with a triad of abdominal pain, peripheral neuropathy, and neuropsychiatric disturbance [4]. Although autonomic instability and electrolyte disturbances, particularly hyponatremia, also occur with regularity [5]. Among these symptoms, the most characteristic symptom, seen in 90% of patients, is a severe, diffuse abdominal pain, often associated with changes in bowel movements [6]. In the case above, there was a presentation with both mood and psychotic symptoms accompanied by subjective reports of myoclonic activity (unconfirmed seizure episodes) and abdominal pain. Peripheral neuropathies secondary to axonal degeneration are also well-documented, occurring in 20% of patients and indicated by proximal muscle weakness, diminution of reflexes, and dysesthesias. Because of the diffuse nature of the presentation and relatively benign lab and imaging findings Table 2, AIP is often mistaken for somatic or factitious disorders. Although, not as common, there are case reports where acute intermittent porphyria can present exclusively with psychosis. As many as 19% to 58% of patients exhibit at least one neuropsychiatric disturbance.

Table 2: An Analysis of 112 Cases of Acute Porphyria in Cape Town Africa [7].

	NO. %
Pain	109(97.3)
Nausea and vomiting	88(78.6)
Hypertension (systolic BP>130)	83(74.1)
Tachycardia (heart rate>100)	42(37.5)
hyponatremia (sodium <135mmol/L	35(31.3)
Constipation	30(26.8)
Psychosis	1(0.9)

Acute attacks, however, can be quite severe and even fatal. It is characterized by severe abdominal pain, autonomic dysfunction, and motor neuropathy that may progress to quadriparesis. This can potentially progress to ileus, hypertension, tachycardia, confusion, seizures, psychosis and eventually a profound flaccid quadriparesis. It is helpful to discern AIP by an extensive history and correlation with either environmental exposures, infectious diseases or other triggers such as menstruation, excessive alcohol consumption, smoking, fasting, prescription drugs, and emotional stress. In patients with an implicated history and remarkable physical examination, the measurement of urine or serum PBG and ALA over 24 hours may confirm the diagnosis. Grossly high levels of PBG may discolor the urine, revealing an amber or 'port wine' colored urine that fluoresces under ultraviolet light. In equivocal cases, diagnosis can be further confirmed through red cell PBGD (Porphobilinogen Deaminase) activity. Though the mainstay of treatment is symptomatic and supportive, definitive diagnosis of AIP is critical to proper management as many common medications are porphyrogenic and may be ineffective or exacerbate the condition further. Moreover, alcohol and cannabis use appear to also precipitate attacks. Moreover, one should consider also that although levodopa, benserazide, and anticholinergic drugs have been used safely in patients with acute porphyria, both lysuride and bromocriptine may precipitate an acute porphyric attack [6]. And in managing psychiatric comorbidities, tricyclic antidepressants and monoamine oxidase inhibitors are contraindicated in porphyria. What is concerning is the conflicting evidence concerning the safety of selective serotonin reuptake inhibitors (SSRIs) in patients with acute intermittent porphyria (AIP). We simply need more data to establish the safety profile of SSRIs and porphyria. For a case of psychotic depression and AIP, ECT was both effective and safe in remitting the patient's psychiatric symptoms while not altering porphyrin levels.

Opiates may be safely administered for pain relief while propranolol may be used to treat sympathetic surge. Finally, in more advanced cases, hemin and other heme oxygenase inhibitors (i.e., tin and zinc metalloporphyrins) may be administered to reduce the synthesis of PBG and ALA. Heme arginate is effective in rapidly reducing ALA and PBG levels in the acute attack, in some cases, one can expect complete resolution of attack within 48 hours heme arginate therapy [7]. Prevention counselling includes alcohol, maintenance of a high carbohydrate diet, and hormonal regulation via oral contraception pills are lifestyle changes that can reduce or prevent an acute crisis. Finally, immediate family members can undergo genetic counselling and testing identify carriers who may also be at risk for this condition.

In conclusion, this case is suggestive of a secondary psychotic disorder as the history was suggestive of episodic psychosis in association with somatic complaints common to acute porphyria. Thus, it would be behoove the consult Psychiatrist to be aware of the somatic correlations of acute porphyria in order to arrive at a precise diagnosis and treatment plan.

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Declaration of Interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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T Patrick Jensen. Biomed J Sci & Tech Res

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