Neuropsychiatric Manifestations of Acute Intermittent Porphyria – A Diagnostic Dilemma

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INTRODUCTION

Porphyrias are a group of inherited or acquired disorders of certain enzymes in the heme bio-synthetic pathway (also called porphyrin pathway). They are broadly classified as acute (hepatic) porphyrias and cutaneous (erythropoietic) porphyrias, based on the site of the overproduction and accumulation of the porphyrins or their chemical precursors. They manifest with either neuropsychiatric complications or skin problems or occasionally both. A clinically induced and histologically identical condition is called pseudo porphyria which is characterized by normal serum and urine porphyrin levels.

The prevalence of all types of porphyria taken together has been estimated to be approximately 1 in 25,000 in the United states.[1] The worldwide prevalence has been estimated to be somewhere between 1 in 500 to 1 in 50,000 people.[2]

HEME BIOSYNTHESIS PATHWAY

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TYPES OF PORPHYRIA

The term derives from the Greek porphyra, meaning "purple pigment". The name is likely to have been a reference to the purple discoloration of feces and urine in patients during an attack.[3] Although original descriptions are attributed to Hippocrates, the disease was first explained biochemically by Felix Hoppe-Seyler in 1874,[4] and acute porphyrias were described by the Dutch physician Barend Stokvis in 1889.[5]

The periodic “madness” of King George III was considered secondary to AIP, in addition to being implicated in Van Gogh's illness and the obstetric history of Queen Anne.

NEUROPSYCHIATRIC MANIFESTATION OF AIP

Acute Intermittent Porphyria [AIP] is the commonest of all porphyria that presented as a medical emergency with substantial mortality [20 %]. The “classical triad” consists of abdominal pain, psychiatric disturbance, and peripheral neuropathies (mostly motor, and often mimicking Guillain-Barré syndrome) during episodes, although psychiatric symptoms alone may be the single presenting feature. Of clinically symptomatic cases, psychiatric disturbance occurs in up to half of all cases, half of which are psychotic episodes, although depression, anxiety, and delirium may also be the main presenting symptoms. The intermittent “attacks” of neuropsychiatric disturbance may result in a misdiagnosis of schizophrenia. How Porphobilinogen [PBG] and Delta Amino Laevulinic Acid
[ALA] accumulation causes neuropsychiatric disturbance is unclear. Explanatory hypotheses have included oxidative stress, vascular change, and demyelination, although it may be that ALA's structural similarity to \( \gamma \)-aminobutyric acid (GABA) results in impaired release of GABA from synapses of GABAergic inhibitory neurons.

**NEUROLOGICAL MANIFESTATION**

1. **Autonomic Dysfunction**
   - Abdominal pain due to splanchnic and vagus nerve involvement
   - Tachycardia
   - Hypertension
   - Constipation
   - Nausea, Vomiting
   - Bladder paresis

2. **Peripheral Neuropathy**
   - Pain in the back/ limbs
   - Muscle weakness
   - Diminished/ absent reflexes
   - Cranial neuropathy
   - Sensory neuropathy
   - Respiratory paresis

3. **Encephalopathy**
   - Seizure
   - Coma
   - Blurred vision
   - Nystagmus
   - Cerebellar ataxia

**PSYCHIATRIC MANIFESTATION**

Mild mental symptoms such as anxiety, depression and insomnia are usually present at the beginning of an acute attack even before abdominal pain develops\(^{[6,7]}\). Aberrant behavior and various psychiatric manifestations like delusion, hallucination, acute transient psychotic episode even schizophreniform psychosis; so-called mental syndrome of acute porphyria\(^{[8]}\) occurs transiently during an acute attack. Frequency of these manifestations has varied from series to series [19\% - 56\%] which may be due to underestimation of mild mental symptoms. In remission, no segregation of acute porphyria and schizophrenia or bipolar disorder has been found in a large
series of 344 AIP patients studied [9]. Anxiety has been reported to be commoner among AIP patients than in the general population [10,11] even in remission.

**TREATMENT**

**GENERAL MANAGEMENT**

**CARBOHYDRATES AND HEME** - Often, empirical treatment are required if the diagnostic suspicion of a porphyria is high since acute attacks can be fatal. A high-carbohydrate diet is typically recommended; in severe attacks, a glucose 10% infusion is commenced. Hematin and Heme Arginate are the drugs of choice in acute porphyria. These drugs need to be given early in an attack. They are not curative drugs but can shorten attacks as well as reduce the intensity. Side effects are rare but can be serious. These heme-like substances theoretically inhibit ALA synthase and hence the accumulation of toxic precursors. Any sign of low blood sodium [hyponatremia] or weakness should be treated as these are signs of impending syndrome of inappropriate antidiuretic hormone [SIADH] or peripheral nervous system involvement that may be localized or severe progressing to bulbar paresis and respiratory paralysis.

**PRECIPITATING FACTORS** - If drugs or hormones have caused the attack, discontinuing the offending substances is essential. Infection is one of the top causes of attacks and requires vigorous treatment.

**SYMPTOM CONTROL** - Pain is severe, frequently out of proportion to physical signs and often requires the use of opiates to reduce it to tolerable levels. Nausea can be severe; it may respond to phenothiazine drugs but is sometimes intractable. Hot water baths/showers may lessen nausea temporarily, though caution should be used to avoid burns or falls.

**NEUROPSYCHIATRIC MANAGEMENT**

**NEUROPATHY** - Patients who experience frequent attacks can develop chronic neuropathic pain in extremities as well as chronic pain in the gut. Gut dysmotility, ileus, intussusception, hypoganglionosis, encopresis in children and intestinal pseudo-obstruction have been associated with porphyrias. In these cases, treatment with long-acting opioids may be indicated. Some cases of chronic pain can be difficult to manage and may require treatment using multiple modalities. Opioid dependence may develop.

**DEPRESSION** - Depression often accompanies the disease and is best dealt with by treating the offending symptoms and if needed the judicious use of anti-depressants. SSRI are the mainstay of treatment, although Paroxetine, Fluvoxamine and Fluoxetine are better be avoided due to their CYP 450 interaction. SNRI like Venlafaxine/ Desvenlafaxine, Mirtazapine can also be used. TCA are better to be avoided due to their significant anticholinergic properties.

**PSYCHOSIS** - For psychotic manifestation, low potency conventional antipsychotics with less anti cholinergic properties like Chlorpromazine, Droperidol; second generation antipsychotic like Olanzapine, Risperidone, Paliperidone, Amisulpiride, Quetiapine are effective options.
Manic or Bipolar symptoms are better controlled with Lithium Carbonate. Levetiracetam and Topiramate are other alternatives, though, efficacy is less. Other conventional mood stabilizers are better avoided keeping in mind the hepatic and cutaneous manifestations of porphyrias including AIP.

**ANXIETY/ INSOMNIA**- Lorazepam, Oxazepam, Temazepam, Triazolam are better choices to combat anxiety or insomnia as hepatic involvement is relatively common in AIP

**SEIZURES**- Seizures often accompany this disease. Most seizure medications exacerbate this condition. Treatment can be problematic: Barbiturates especially must be avoided. Some benzodiazepines are safe and, when used in conjunction with newer anti-seizure medications such as Gabapentin, offer a possible regime for seizure control. Magnesium Sulfate and Bromides have also been used in porphyria seizures, however, development of status epilepticus in porphyria may not respond to Magnesium alone. The addition of Hematin or Heme Arginate has been used during status epilepticus.

**CONCLUSION**

AIP with its associated neuro psychiatric manifestations poses a great diagnostic dilemma to physician, neurologists, and psychiatrists due to significant symptom overlap. The neurological symptoms often mimic other types of neuropathy, radiculopathy Guillain-Barry syndrome. Combination of photodermatitis, neurological and psychiatric manifestation are also seen in many autoimmune diseases like SLE, Dermatomyositis, Polymyositis etc. A great deal of suspicion, hematological and urine/ stool examination for precursors and early management are the mainstay to combat such deadly emergency.
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