Case Reports

Acute Intermittent Porphyria: Some Diagnoses are Only Made If Thought of

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Key Learning Points
- AIP has a diverse range of presentations and may affect multiple systems and hence present to a variety of specialities – all should be aware of the condition.
- There are a multitude of recognised triggers which should be sought and eliminated through patient education.
- AIP is a rare condition but eminently treatable and therefore important not to miss. The diagnosis will only be made if thought of.

Case Report

A 20-year-old Asian, female, student nurse of thin body habitus (Body Mass Index 16.5) but otherwise previously well had numerous admissions to our centre under a variety of surgical sub-specialities over a 5-month period. Each month, coinciding with menses, she complained of non-specific abdominal discomfort in the absence of any other symptoms. With the exception of the presence of a sinus tachycardia coupled with incidental hyponatraemia full physical examinations and routine baseline investigations were unremarkable.

She underwent comprehensive investigation including two abdominal ultrasound scans, a computed tomogram of the abdomen and pelvis and a Magnetic Resonance Cholangiopancreatogram. No culprit pathology was identified and a functional aetiology was suspected.

A subsequent similar admission under the Gynaecology Team prompted a diagnostic laparoscopy which demonstrated mild endometriosis. She was commenced on the combined oral contraceptive pill (COCP). Her post-operative course was complicated by acute urinary retention and two self-terminating tonic-clonic seizures attributed to progressive hyponatraemia secondary to the syndrome of inappropriate anti-diuretic hormone (SIADH). Cerebral imaging was normal.

Ultimately, 8-months after her first presentation, she was admitted under the medical team with similar complaints. Following a detailed review of her case records a diagnosis of acute intermittent porphyria (AIP) was suspected and confirmed on biochemical screening.

Her COCP was stopped and she was commenced on propanolol. She was referred to a specialist centre where she was treated with Haem Arginate with good clinical and biochemical effect.

Acute Intermittent Porphyria – a literature review

Aetiology and Epidemiology

The porphyrias are a disease group caused by deficiencies in the activities of enzymes within the haem biosynthetic pathway. Although still rare, AIP is the most common acute form and can be severely debilitating. It results from a partial deficiency of the hepatic enzyme porphobilinogen deaminase (PBGD) which results in accumulation and excess urinary excretion of porphobilinogen (PBG) and aminolevulinic acid (ALA). The gene for PBGD is located on chromosome 11. Inheritance is autosomal dominant but penetrance is variable and of those affected the majority do not exhibit clinical disease.[1,2,3]

The incidence of symptomatic disease is highest in the U.K. and Scandinavia and is estimated at 1–2 per 100,000 people.[3] It is more common in females with onset typically in the third decade while in males onset is usually in the fourth decade.[4]

Clinical Features

AIP characteristically presents as recurrent 'attacks' affecting multiple systems. These may vary in severity, duration (from days to months) and frequency both between and within individuals. Neurological dysfunction, affecting any of the central, peripheral or autonomic system, is central to the majority of features.

The most common manifestation is abdominal discomfort, occurring in 85–95%.[5] Pain may be localised or generalised and can be accompanied by guarding, raising the suspicion of an acute abdomen. Often large doses of opiates are required and it is common for patients to undergo abdominal imaging and even unnecessary surgical intervention.

Other systems affected and features that may be encountered are shown in Table 1.

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Gastrointestinal	Nausea, Vomiting, Constipation, Diarrhoea, Abdominal Distension
Genitourinary	Urinary Retention, Incontinence, Dysuria
Neurological	Peripheral Neuropathy (predominantly motor), Cranial Nerve Palsies, Seizures, Weakness, Tremor, Altered Consciousness, Coma
Cardiovascular	Tachycardia, Hypertension
Psychiatric	Anxiety, Depression, Agitation, Hallucinations, Histrionic Behaviour
Other	Pyrexia, Sweats

Table 1. System Based Manifestations of AIP.

Antibiotics	Aminoglycosides, Sulphonamides, Isoniazid, Ciprofloxacin, Penicillins, Tetracyclines
Anti-fungals	Griseofulvin, Actinomycin-D
Analgesics	Fentanyl, Ibuprofen, Ketoprofen
Anti-epileptics	Phenytoin, Clobazam, Sodium Valproate
Psychotropics	Barbiturates, Chlordiazepoxide, Diazepam, Fluoxetine, Lofepramine, Promazine
Cardiac Drugs	Digoxin,
Oestrogens	Oral Contraceptive Pill

Table 2. Medications Implicated In Provoking An Acute Attack.

Seizures occur in 10–20%[5] and in the context of AIP are usually attributed to hyponatraemia (due to inappropriate intravenous fluids, SIADH or excess renal sodium excretion)[6] but may occur in those with a normal biochemical profile.

A peripheral neuropathy may develop. This is usually predominantly motor but if there is sensory involvement, it is often in a 'bathing trunk' distribution.[7] During an acute attack, muscular weakness can progress rapidly resulting in limb paralysis and even respiratory failure, requiring intubation and ventilation. With recurrent attacks, neuropathy may become permanent.

Tachycardia, which is often disproportionate to clinical wellbeing, is the most common physical sign, encountered in up to 80% of patients.[8]This may be driven by either autonomic neuropathy or a catecholamine surge during an acute attack and can precipitate cardiac dysrhythmias and sudden death.[9]

Psychiatric symptoms are evident in 40–58% of cases[5] and may dominate the clinical picture leading to a misdiagnosis of personality disorder, hysteria, depression or even schizophrenia.[10] Generalised anxiety is the most preponderant manifestation and the level of anxiety has been shown to correlate significantly with the level of porphyrin metabolites in the urine.[11]

Precipitants

Both endogenous and exogenous factors promote the induction of ALA synthase, the rate-limiting enzyme of the haem biosynthetic pathway, and this together with reduced PBGD activity in patients with AIP may result in an acute attack. Precipitants include:

- Medications
- Poor Carbohydrate Load – Fasting, Dieting, Malnutrition
- Hormonal Changes–Pre-menstruation and Pregnancy
- Sepsis
- Substance Misuse–Cocaine, Ecstasy, Amphetamines, Marijuana
- Smoking
- Alcohol
- Emotional and Physical Stress (Including surgery)

On occasion, no precipitant is identified.

Diagnosis

AIP can be diagnosed when the clinical picture correlates with laboratory findings. An acute attack results in elevated excretion of ALA and PBG. Polymerisation of the latter may cause urine to be discoloured red/brown on standing. Urine should be collected over a twenty four hour period, protected from light, and sent to the laboratory to measure ALA and PBG. If results are equivocal it may also be necessary to measure faecal and plasma porphyrins.[1]

Treatment

Treatment of Acute Attacks

Supportive Therapy

Typically, hospital admission for regular assessment allowing early treatment of the recognised complications is necessary. Provoking medications should be withdrawn and only those known to be safe should be prescribed. Many lists of 'safe' and 'unsafe' drugs[12,13,14] exist and these should be referred to. However, no one list is universally accepted.

Intravenous fluids, analgesia and anti-emetics (chlorpromazine, prochlorperazine and metoclopramide are safe) are usually required together with vigilant electrolyte monitoring. Propanolol can be helpful for treating hypertension and tachycardia.

Intercurrent infection should be sought and promptly treated.

Seizures are difficult to treat as many conventional anti-epileptic agents are recognised precipitants[15]. Vigabatrin and gabapentin are effective agents and are not porphyrogenic.[16] Prior optimisation of electrolyte imbalances is crucial.

Reduction of Activation of ALA Synthetase

An adequate calorie intake must be maintained – a minimum daily intake of 300g of carbohydrate is required during acute attacks.[2] This may prove difficult in the presence of abdominal pain and nausea and alternative methods of calorie delivery may need consideration, in particular, nasogastric feeding or intravenous dextrose.[8] In extreme cases, total parenteral nutrition (TPN) may be necessary.

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Intravenous haem products (haemin and haem arginate) suppress hepatic ALA synthetase, preventing the overproduction of ALA and PBG. This should be commenced early in an acute attack,[17] particularly if neurological features are apparent. It is given daily for 4 days and improvement is usually dramatic within one week.

Prevention of Acute Attacks

Patient education is paramount and in particular they should be alerted to the avoidance of the many precipitating factors. Furthermore, patients should be encouraged to wear a medic-alert bracelet and referred to a specialist centre.

In those with recurrent pre-menstrual attacks, a luteinizing hormone releasing hormone (LHRH) analogue, which induces a chemical menopause, may be considered.[18] Bone protection measures should be implemented in these circumstances.

Definitive Therapy

Liver transplantation has been performed with dramatic biochemical and clinical response. It is reserved for extreme cases refractory to standard therapy.[19]

Family Screening

All first degree relatives should be offered screening to identify at risk individuals.

Prognosis

AIP can be life-threatening. A three-fold increase in mortality in patients with symptomatic AIP compared to the general population has been observed with the majority of deaths occurring during an acute attack.[20] Suicide is 370-times more prevalent than in the general population and is thought to reflect the pain experienced and psychiatric manifestations of AIP.[20]

Long-term sequelae include secondary hypertension (with 40% of patients remaining hypertensive between attacks),[5] renal failure (the aetiology of which is unknown but hypertension may be implicated[21]) and hepatocellular carcinoma.[22]

Conclusion

Our case is a typical presentation of AIP. There was a significant delay to diagnosis preceded by multi-speciality over-investigation spanning several admissions. A diagnosis was established only because the possibility was entertained following thorough review and reflection of her case. Retrospectively, this highlighted multiple precipitating factors associated with her episodic and cyclical disease course. Ultimately, it was an unexplained persistent tachycardia disproportionate to her well-being and multidisciplinary suspicion of psychogenic and functional disease which prompted investigation for AIP.

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