

The Atkins™ Diet as a Possible Trigger for an ICU Admission: A Case Report

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ABSTRACT

A case of initial presentation and diagnosis of hereditary coproporphyrria is described, following a patient's first seizure in the surgical ward, where she had been admitted for investigation of abdominal pains. The frequency of seizures, motor neuropathy and florid visual hallucinations worsened over the subsequent days, until the definitive investigations revealed the diagnosis and specific therapies were instituted.

The acute porphyrias, a rare group of conditions caused by deficiencies in enzymes involved in haem biosynthesis, are associated with significant morbidity and occasional mortality. Consideration of the diagnosis, combined with appropriate supportive and specific therapies can reduce the duration of the crisis and lessen the rates of morbidity and mortality associated with these conditions. (Critical Care and Resuscitation 2003; 5: 193-197)

Key words: Hyponatraemia, porphyria, porphyrins, haem

The acute porphyrias can present with a confusing array of symptoms, involving almost every organ system. The diagnosis must be entertained, particularly when inexplicable hyponatraemia occurs in the setting of abdominal pain. Cessation of drugs and loading with carbohydrate may ablate an acute attack. If it continues despite these measures, rapid administration of haem preparations may be life saving.

A case is presented which highlights the rare condition of acute porphyria, in this example, the extremely rare hereditary coproporphyrria. The history of chronic non-specific abdominal pain combined with symptoms and signs such as the seizures, hallucinations and subsequent motor neuropathy, accompanying the severe hyponatraemia suggested the diagnosis and allowed for prompt supportive and specific treatment. The patient recovered without significant clinical sequelae.

CASE REPORT

A 49-year-old lady was admitted to the surgical ward with a provisional diagnosis of acute cholecystitis. She had been experiencing worsening epigastric pain over

the preceding five days. Her previous medical history included hypothyroidism (now euthyroid on supplementation) and a hysterectomy for menorrhagia. On examination her abdomen was soft and non-tender. There were no masses or organ enlargement. She was afebrile and normotensive. The ESR and white cell count were 5 mm/hr and $7 \times 10^9/L$ respectively. Plasma sodium was 137 mmol/L. Plasma lipase was normal. Abdominal ultrasound revealed a small contracted gall bladder with multiple calculi. There was no duct dilation.

Intravenous 4% dextrose and 1/5 N saline was commenced at 60 mL/hr. That night the patient was transferred to the intensive care unit after two self-limiting tonic-clonic seizures. She was afebrile and normotensive, with pulse oximetry revealing a SpO₂ of 93% while breathing air. There was no neck stiffness and her neurological examination was normal apart from a Glasgow Coma Score of 13. Her blood glucose level was 6.4 mmol/L. The plasma sodium had decreased to 125 mmol/L. A CT scan of her head was within normal limits.

Phenytoin 17 mg/kg was administered intravenously and a serum magnesium level of 0.7 mmol/L was

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supplemented with 20 mmols of MgSO₄ intravenously. Fluid restriction was commenced, the infusion changed to normal saline at 40 mL/hr, and measurements of serum sodium were repeated throughout the evening. On further questioning, the patient described a long history of intermittent, diffuse abdominal pain that had been attributed to gall stones. The most recent exacerbation coincided with initiation of a high protein and low carbohydrate diet (Atkins Diet™).

The following morning, the plasma sodium was 129 mmol/L. Her neurological examination revealed no abnormalities and she was discharged to the care of a physician. Later that day a further grand mal seizure was witnessed. The plasma sodium at this stage was 134 mmol/L and the plasma glucose was 7.9 mmol/L. After the seizure the patient was noted to be persistently hyperreflexic, with fast nystagmus on leftward gaze. An MRI showed scattered subcortical white matter hyperintensities, some with peri-vascular enhancement. An EEG was performed which showed no alpha activity, with high amplitude irregular delta and theta waves which generalised intermittently.

On readmission to the ICU, the patient displayed generalised weakness and hyporeflexia. She was unable to stand and was experiencing florid visual and auditory hallucinations. Urinary sodium from the previous evening was 125 mmol/L, with a measured plasma osmolality of 240 mmol/L. Over the next twenty-four hours the plasma sodium reduced to a nadir of 117 mmol/L despite fluid restriction. Plasma and urinary porphyrin screens, requested during her initial admission to the ICU, revealed a urinary porphyrin/creatinine ratio of 1316 (normal <35), and urinary porphobilinogens were detected. Plasma porphyrins were elevated at 29.2 nmol/L (normal < 10 nmol/L). Accordingly, after high dose oral and intravenous 50% dextrose, Panhematin™ (Abbott Laboratories Chicago, Illinois) was administered at 4 mg/kg/day for 5 days.

By day 3, her cognition began to improve. On day 4 the visual and auditory hallucinations were diminishing. On day 5, she had regained enough power in her lower limbs to stand. The nystagmus had also disappeared and she was transferred to the ward on day 5, and discharged home the following day. Her plasma sodium on discharge was 136 mmol/L. The abdominal pain had disappeared completely for the first time in years.

Two weeks later, her motor power was completely normal. Faecal porphyrins were elevated at 5600 nmol/24 hr (normal < 200 nmol/24 hr), with an elevated coproporphyrin III:I ratio of 14.5. Porphobilinogen deaminase (PBGD) activity was 490 mv/L (340 - 695 mv/L). The patient was told that she was suffering from hereditary coproporphyrin (HCP). On subsequent family screening it was found that her sister and one of her

daughters also had the condition, although they had never suffered any symptoms.

DISCUSSION

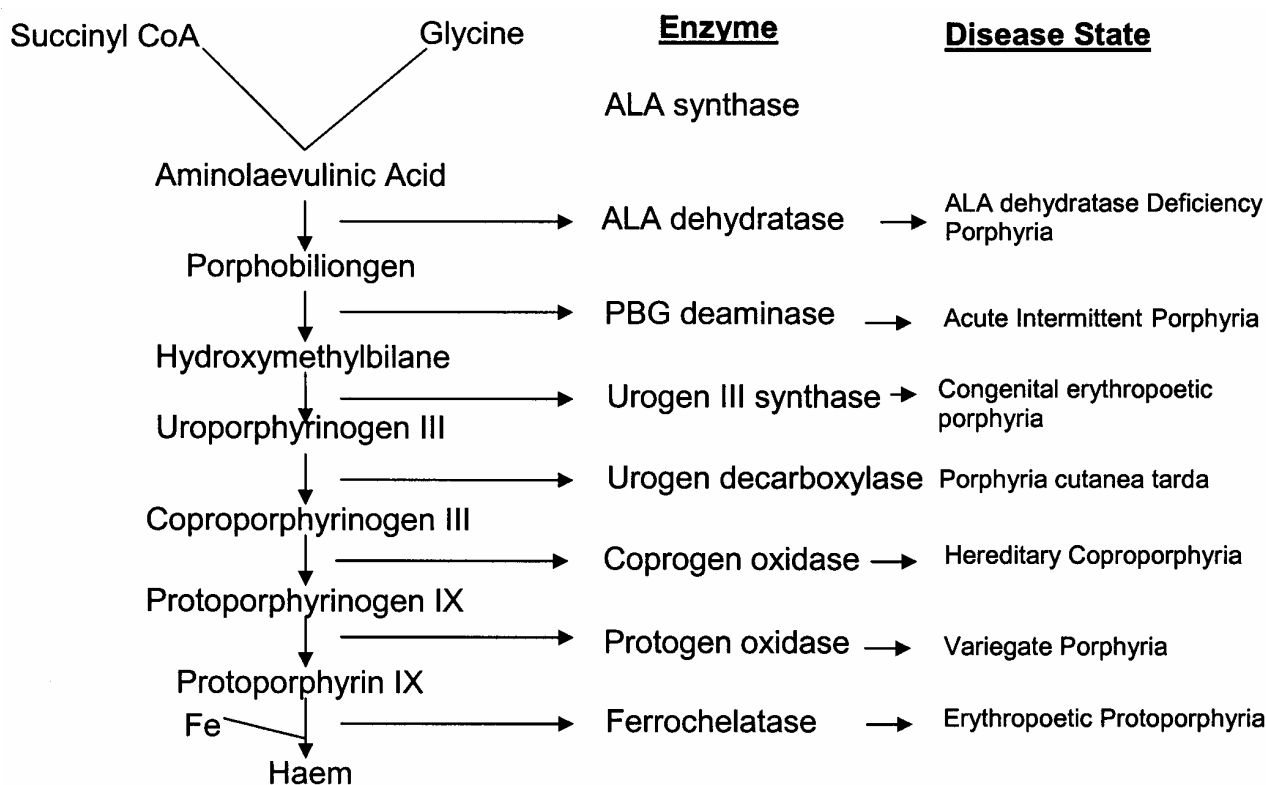
In this patient the normal PBGD level excluded the diagnosis of acute intermittent porphyria (AIP). The elevated faecal porphyrins, with a high coproporphyrin III:I ratio confirmed that she had hereditary coproporphyrin.

The porphyrias are disorders of haem biosynthesis in which overproduction of specific haem precursors are associated with characteristic neurovisceral and cutaneous clinical features.¹ Each porphyria is the result of a decrease in the activity of one of the enzymes in haem biosynthesis (Figure 1). There are eight enzymes involved in the pathway and an enzymatic defect at every step (except the first) can lead to tissue accumulation and excessive excretion of porphyrins and their precursors.¹ In the non-porphyrin individual, production of the haem molecule provides negative feedback by inhibiting aminolaevulinic acid (ALA) synthase and hence inhibits excess production of haem (itself physiologically very important but toxicologically irrelevant) or its precursors (physiologically irrelevant but severely toxic, should they accumulate). Synthesis of porphyrins occurs in nearly all living cells, both animals and plant, where they are the precursors of haem and chlorophyll respectively.²

Hereditary coproporphyrin (HCP) is an autosomal dominant hepatic porphyria with predominantly neurovisceral manifestations due to the deficient activity of coproporphyrinogen oxidase.³ Cutaneous symptoms do occasionally occur.⁴ Clinically expressed HCP is much less common than other clinically expressed acute hepatic porphyrias. The incidence of HCP is estimated at two cases per million, compared with the incidence of AIP, which is estimated at 1 - 8 per 100 000.⁵

Although specific enzyme deficiencies are required to produce AIP, HCP and variegate porphyria (VP), approximately 90 percent of individuals with a deficiency of one of these enzymes remain biochemically and clinically normal throughout life.⁶ Development of the disease state depends on factors that increase the activity or concentration of ALA synthase, which catalyses the rate limiting step in hepatic haem biosynthesis. Increased activity of ALA synthase, in combination with the specific enzyme deficiency (PBGD in AIP, coproporphyrinogen oxidase in HCP, or protoporphyrinogen oxidase in VP), causes accumulation of the porphyrin precursor ALA and subsequent precursors to haem, and hence induces the acute attack.

There are at least five different classes of precipitating factors. Commonly, however, no inducer of an attack is found.



ALA = aminolaevulinic acid, PBG = porphobiliongen, Urogen = uroporphyrinogen, Coprogen = coproporphyrinogen, Protopogen = protoporphyrinogen.

Figure 1. Enzymatic aetiology of human porphyrias.

Endocrine factors. The clinical diseases of acute hepatic porphyrias are more common in women, especially during the premenstrual phase. A subset of women experience cyclical premenstrual exacerbations of the disease.⁷ The oral contraceptive pill can also induce a porphyric crisis.^{8,9}

Caloric intake. Inadequate nutrition, specifically carbohydrate, induces hepatic microsomal haem oxygenase.¹⁰ This results in decreased hepatic haem concentrations, loss of haem repression of ALA synthase and the onset of clinical symptoms.

Drugs and chemicals. Drugs which induce the cytochrome P₄₅₀ system increase the demand for haem synthesis, leading to induction of hepatic ALA synthase, and thereby exacerbating the disease.

Stress. Physiological stressors, such as intercurrent illnesses, infections, alcoholic excess and surgery upregulate the haem oxygenase gene leading to exacerbations of acute porphyrias.¹⁰

Smoking. Chemicals in tobacco smoke are known inducers of hepatic cytochrome P₄₅₀ enzymes and haem synthesis.¹¹ An association between cigarette smoking and repeated attacks of porphyria has been described.

Hence, smoking cessation may reduce the incidence of acute attacks.

Clinical features

Acute attacks of AIP, VC and HCP are usually clinically indistinguishable. Both VC and HCP can have cutaneous signs but these are much less common than the neurovisceral symptoms in HCP. The acute porphyrias are expressed clinically only after puberty, and more commonly in women, particularly in the week preceding menses. Abdominal pain, which may be generalised or localised, is the most common symptom and is often the initial sign of an acute attack. Other gastrointestinal features include nausea, vomiting, constipation or diarrhoea and ileus. Urinary retention and incontinence are also common, and tachycardia, hypertension, and, less frequently, fever, sweating, restlessness and tremor may be found. In up to 40% of patients, hypertension is sustained even in convalescent periods. Peripheral neuropathy, particularly motor neuropathy (as was observed in our case), is common. Muscle weakness generally begins in the legs but can involve upper limbs. Motor neuropathy may also

involve the cranial nerves and can result in bulbar paralysis, respiratory embarrassment, and death.

Acute attacks may be accompanied by seizures, especially as patients are prone to hyponatraemia, due to vomiting, inappropriate fluid therapy or the syndrome of inappropriate anti-diuretic hormone release (SIADH). This can be a self-perpetuating circle, as most anticonvulsants and some benzodiazepines are potential precipitants of an acute attack. The course of an acute attack of porphyria is highly variable within a single individual as well as among patients, lasting from a few days to several months.

Psychiatric complaints may be prominent, and may even represent the sole manifestation of the disease.¹² There is a high incidence of previously undiagnosed porphyria in the psychiatric population. Symptoms are myriad, but include hysteria, florid hallucinations, depression, phobias, psychosis, agitation, delirium, and altered consciousness, ranging from somnolence to coma.¹³

Pathophysiology of acute porphyria

The exact pathophysiology of the acute porphyrias and their multiple symptoms remains unclear, but there is some evidence for a combination of non-exclusive mechanisms. For example, a direct neurotoxic effect of the porphyrin precursors, in particular ALA and PBG.¹⁴⁻¹⁷

- ALA promotes the generation of reactive oxygen species (ROS) *in vitro* which may result in oxidative damage to membrane structures within the central nervous system.¹⁸
- Inhibition by ALA of gamma-aminobutyric acid (GABA) release at central synapses.²
- Deficiency of haem in the central nervous system, which may retard synthesis of haemoproteins such as cytochrome P₄₅₀ or nitric oxide synthase.¹

Investigations

When neurovisceral symptoms suggestive of hepatic porphyria are present, urinary ALA, porphobilinogen, and plasma and faecal porphyrin concentrations should be requested. Urinary measurements are conducted on an aliquot from a 24-hour urine collection and reported as a porphobilinogen/creatinine ratio. Normal PBGD levels in the face of elevated porphyrins and presence of faecal porphyrins excludes AIP, and combined with the elevated faecal corpporphyrins with inversion of corpporphyrin I:III ratio, is classical of HCP.²

Management

Management of acute porphyria is two-fold, involving prevention of future attacks as well as treatment of the current episode.

Preventive measures include adequate nutritional intake, avoidance of drugs and chemicals known to exacerbate porphyria, and prompt treatment of intercurrent diseases or infections. Nasal or subcutaneous administration of long-acting agonistic analogues of LHRH inhibit ovulation and greatly reduce the incidence of peri-menstrual attacks.¹⁹ A prophylactic weekly transfusion of haem preparations has been administered to patients who suffer severe and frequent exacerbations.²⁰

Treatment of the acute attack entails a number of components:

- All medications that can exacerbate the hepatic porphyrias must be stopped immediately. (See <http://www.uq.edu.au/porphyria/>). Any drug that is dependant on cytochrome P₄₅₀ metabolism, even if listed as safe, should be avoided if possible. Knowledge about the safety of many drugs and other over-the-counter preparations is incomplete.
- Careful fluid management is important. Correction of electrolyte disturbances, especially acute hyponatraemia, should be carried out promptly. Hypertension and pain must be aggressively treated. Patients with frequent porphyric crises may require very large doses of opiates due to tolerance.
- Bedside spirometry should be available to detect early bulbar paralysis. A falling vital capacity may herald the need for mechanical ventilation.

Severe cases should be treated with intravenous administration of dextrose to provide a minimum of 400 g of carbohydrate/day.²¹ Effective caloric intake may abort an attack, possibly due to the fact that glucose inhibits hepatic ALA synthase activity via an uncertain mechanism.²¹ Acute porphyrias frequently induce vomiting and severe ileus, hence oral intake of carbohydrates may not be feasible.

Intravenous haem preparations

The use of intravenous haem preparations, to repress ALA synthase activity, reduces ALA and subsequent porphyrin excretion and is effective in curtailing acute neurovisceral symptoms in the hepatic porphyrias.²² Haem preparations should be administered if there has been unsatisfactory improvement of the acute attack following the administration of carbohydrate for at least two days. However, they may be life-saving when employed early in severe attacks, especially those accompanied by bulbar paralysis.²³ Early use, when neuronal damage is still reversible, may also help to avoid incomplete motor recovery.

In Australia, the haem preparation that is available is Panhematin™. It is supplied as a dried powder, which is reconstituted with sterile water immediately before injection. The recommended initial dose is 3 to 4 mg/kg intravenously given over 10 to 15 minutes. This is

repeated once daily for at least three days. Some believe that there is no additional benefit to be gained beyond 5 days of therapy. The haem molecule has a relatively short half-life and the therapy can be repeated if there are relapses.

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REFERENCES

- Anderson KE, Sassa S, Bishop DF, Desnick RJ. The porphyrias. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. *The metabolic basis of inherited disease*, 8th ed. vol. 1. New York: McGraw-Hill; 2001. p. 2991-3062.
- Nordmann Y, Puy H. Human hereditary hepatic porphyrias. *Clinica Chimica Acta* 2002;325:17-37.
- Rosipal R, Lamoril J, Puy H, Da Silva V, Gouya L, De Rooij FW, et al. Systematic analysis of coproporphyrinogen oxidase gene defects in hereditary coproporphyria and mutation update. *Human Mutat* 1999;13:44-53.
- Lamoril J, Puy H, Whatley SD, Martin C, Woolf JR, Da Silva V, et al. Characterization of mutations in the CPO gene in British patients demonstrates absence of genotype-phenotype correlation and identifies relationship between hereditary coproporphyria and harderoporphyria. *Am J Hum Genet* 2001;68:1130-1138.
- May A, Bishop DF. The molecular biology and pyridoxine responsiveness of X-linked sideroblastic anaemia. *Haematologica* 1998;83:56-70.
- McColl KE, Wallace AM, Moore MR, et al. Alterations in haem biosynthesis during the human menstrual cycle: Studies in normal subjects and patients with latent and active acute intermittent porphyria. *Clin Sci* 1982;62:183-191.
- Welland, FH, Hellman ES, Gaddis EM, et al. Factors affecting the excretion of porphyrin precursors by patients with acute intermittent porphyria. I. The effects of diet. *Metabolism* 1964;13:232.
- Levit, EJ, Nodine JH, Perloff WH. Progesterone-induced porphyria. *Am J Med* 1957;22:831.
- Rodgers PA, Stevenson DK. Developmental biology of heme oxygenase. *Clin Perinatol* 1990;17:275-291.
- Lip GY, McColl KE, Goldberg A, et al. Smoking and recurrent attacks of acute intermittent porphyria. *BMJ* 1991;302:507-508.
- Tishler PV, Woodward B, O'Connor J, et al. High prevalence of intermittent acute porphyria in a psychiatric patient population. *Am J Psychiatry* 1985;142:1430-1436.
- Burgovne K, Swartz R, Ananth J. Porphyria: Re-examination of psychiatric implications. *Psychother Psychosom* 1995;64:121-130.
- Pierach CA, Edwards PS. Neurotoxicity of delta-aminolevulinic acid and porphobilinogen. *Exp Neurol* 1978;62:810-814.
- Bechara EJ. Oxidative stress in acute intermittent porphyria and lead poisoning may be triggered by 5-aminolevulinic acid. *Braz J Med Biol Res* 1996;29:841-849.
- Puy H, Deybach JC, Bogdan A, et al. Increased delta aminolevulinic acid and decreased pineal melatonin production. A common event in acute porphyria studies in the rat. *J Clin Invest* 1996;97:104-110.
- Shanley BC, Neethling AC, Percy VA, et al. Neurochemical aspects of porphyria. Studies on the possible neurotoxicity of delta-aminolaevulinic acid. *S Afr Med J* 1975;49:576-580.
- Princ FG, Juknat AA, Amitrano AA, Batlle A. Effect of reactive oxygen species promoted by delta-aminolevulinic acid on porphyrin biosynthesis and glucose uptake in rat cerebellum. *Gen Pharmacol* 1998;31:143-148.
- Brennan MJ, Cantrill RC. Delta-aminolaevulinic acid and amino acid neurotransmitters. *Mol Cell Biochem* 1981;38 Spec No(Pt 1):49-58.
- Anderson KE, Spitz IM, Sassa S, et al. Prevention of cyclical attacks of acute intermittent porphyria with a long-acting agonist of luteinizing hormone-releasing hormone. *N Engl J Med* 1984;311:643-645.
- Mustajoki P, Tenhunen R, Pierach C, Volin L. Heme in the treatment of porphyrias and hematological disorders. *Semin Hematol* 1989; 26: 1-9.
- Doss M, Sixel-Dietrich F, Verspohl F. "Glucose effect" and rate limiting function of uroporphyrinogen synthase on porphyrin metabolism in hepatocyte culture: relationship with human acute hepatic porphyrias. *J Clin Chem Clin Biochem* 1985;23:505-513.
- Lamon JM, Frykholm BC, Bennett M, Tschudy DP. Prevention of acute porphyric attacks by intravenous haematin. *Lancet* 1978;8088:492-494.
- Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. *Arch Intern Med* 1993;153:2004-2008.