Clinical Medicine 2012, Vol 12, No 3: 293–4

lesson of the month (1)

Acute intermittent porphyria: fatal complications of treatment

Acute neurovisceral attacks of porphyria can be life threatening. They are rare and notoriously difficult to diagnose clinically, but should be considered, particularly in female patients with unexplained abdominal pain, and associated neurological or psychiatric features or hyponatraemia. The diagnosis might be suggested by altered urine colour and can be confirmed by finding an elevated porphobilinogen concentration in fresh urine protected from light. Severe attacks require treatment with intravenous haem arginate and supportive management with safe drugs, including adequate analgesia. Intravenous glucose in water solutions are contraindicated as they aggravate hyponatraemia, which can prove fatal.

Lesson

A 17-year-old schoolgirl was referred to her local hospital with a five-day history of general malaise, vomiting, constipation, abdominal pain and aching in her legs. Her last menstrual period had been three weeks earlier. Her past medical history was unremarkable and no relevant family history was identified. She was taking no medication. She had drunk alcohol occasionally and had had several alcoholic drinks at a party on the evening before her symptoms started. On examination she was apyrexial; her pulse was 96 beats per min, her blood pressure was 130/85 mmHg and there was generalised abdominal tenderness without rebound or guarding. Cardiorespiratory and neurological examinations were normal. Full blood count was normal. Her serum sodium was 133 mmol/l (136–144). Liver-related tests were normal. The provisional diagnosis was a viral illness. She was admitted for monitoring and treated with analgesic and antiemetic drugs.

PE Stein,[1] clinical fellow in metabolic medicine; **MN Badminton,**[2] senior lecturer, honorary consultant in biochemistry; **JH Barth,**[3] consultant in chemical pathology and metabolic medicine; **DC Rees,**[4] senior lecturer, honorary consultant in haematological medicine; **R Sarkany,**[5] consultant in dermatology; **MF Stewart,**[6] consultant in clinical biochemistry; **TM Cox,**[1] professor of medicine, honorary consultant physician

[1]University of Cambridge, Addenbrooke's Hospital; [2]Hospital of Wales, Cardiff; [3]Leeds General Infirmary; [4]King's College Hospital NHS Foundation Trust; [5]Guy's and St Thomas' NHS Foundation Trust; [6]Salford Royal NHS Foundation Trust

Over the following few days, the patient complained of increasing leg weakness and was noted to be anxious and confused. She remained tachycardic with episodes of hypertension. By day six of her admission, her serum sodium had fallen to 129 mmol/l. One week after admission, nursing staff noted dark-red urine and a screening test for porphobilinogen was strongly positive, indicating acute porphyria. Intravenous glucose 5% was started on day eight, but was stopped after a few hours when her serum sodium was found to be 116 mmol/l. Later that day, she had hallucinations. On day nine, her serum sodium remained low at 115 mmol/l. Fluids were restricted and glucose 50% was infused through a central venous line. On day 10 she had a respiratory arrest and was transferred to the intensive care unit, but died shortly after. A post-mortem found cerebral oedema with herniation of the cerebellar tonsils.

Further analysis of the patient's urine confirmed biochemical changes consistent with acute porphyria. Subsequent family screening, including molecular analysis of the hydroxymethyl bilane synthase gene, identified a pathogenic sequence variant, which has previously been described in patients with acute intermittent porphyria, including her mother, brother and maternal grandmother. None of these relatives had had a documented acute attack.

Discussion

The acute porphyrias (acute intermittent porphyria (AIP); variegate porphyria (VP); and hereditary coproporphyria (HCP)) are dominantly inherited disorders of haem synthesis.[1] Gene carriers have a combined prevalence of approximately 1 in 10,000 in the UK population. Most remain asymptomatic, but approximately 10% present with acute neurovisceral attacks. Motor, autonomic and/or central nervous systems can be affected, presumably as the result of accumulation of neurotoxic porphyrin precursors. Patients with VP or HCP can experience light-sensitive skin disease, either separately or during an attack.

Acute attacks are most common in young adults and affect women more than men. They are extremely rare before puberty and unusual after the menopause. Most attacks are triggered by unsafe medication or by hormonal changes. Other precipitating factors include dieting or fasting, alcohol (particularly binge drinking), infections and stress. In this patient, alcohol was probably the initial trigger, particularly in the luteal phase of her menstrual cycle, but the attack was exacerbated by the administration of porphyrinogenic drugs given before the diagnosis of porphyria was made.

The presenting complaint in an acute attack is usually abdominal pain that is severe and poorly localised. However, pain can affect other sites, especially the back and legs. Nausea, vomiting

and constipation are typical. Other features include tachycardia, hypertension, psychiatric manifestations (including agitation, insomnia, confusion and psychosis), seizures (which might be related to hyponatraemia) and muscle weakness. In severe cases, there can be flaccid paralysis and respiratory insufficiency. Urine darkens to an orange or red colour on exposure to light owing to formation of oxidised porphyrins. Hyponatraemia is also frequent; the mechanism is poorly understood but includes inappropriate secretion of antidiuretic hormone and renal sodium loss.

Although the clinical symptoms are non-specific, the diagnosis of an acute attack of porphyria can be readily confirmed by demonstrating increased porphobilinogen (and aminolevulinic acid) concentration in a light-protected sample of urine collected while symptoms are present. Often the diagnosis is not considered until the attack is established, as described here.

Once the diagnosis has been made, it is important to remove all potential precipitating factors. In particular, all medication must be checked for safety. The Welsh Medicines Information Centre provides advice and a list of drugs considered safe in acute porphyria (www.wmic.wales.nhs.uk/porphyria_info.php) and The Norwegian Porphyria Centre (NAPOS) website offers information about specific drugs (www.drugs-porphyria.org). Management involves supportive treatment, including adequate analgesia. Fluid balance and electrolytes should be closely monitored, and hyponatraemia corrected appropriately with sodium-containing fluids. Fluid restriction is not usually indicated.

Patients with severe attacks (ie severe or prolonged pain, persistent vomiting, hyponatraemia, seizures, psychosis or neuropathy) require specific treatment with haem arginate.[2] This is available as Normosang™ (Orphan Europe, UK), and should be diluted immediately before use in sodium chloride 0.9%. The dose is 3 mg/kg daily (to a maximum of 250 mg daily) on four consecutive days infused over 30–60 min via a large antecubital vein or central line, followed by thorough flushing with sodium chloride 0.9% to prevent phlebitis. Haem arginate has been administered in pregnancy and appears safe.[3,4]

Glucose inhibits haem synthesis[5] and carbohydrate loading was used to treat acute attacks before haem arginate became available. Mild attacks can be managed with a high carbohydrate diet and supportive measures. Patients who are not tolerating oral nutrition can be given intravenous sodium chloride 0.9% containing glucose 5% at a rate of 2 l/24 h.[1,6] However, all intravenous glucose in water solutions should be avoided as they potentiate hyponatraemia and its osmotic effects. In this case, the patient did not receive haem arginate and the administration of hypotonic intravenous glucose solutions in the context of profound hyponatraemia contributed to her death. With early diagnosis and appropriate treatment, deaths from acute attacks of porphyria should be very rare.

From 1 April 2012 a National Acute Porphyria Service has been commissioned for patients living in England. The service is provided by three main centres in Cardiff, Cambridge and London (Kings College Hospital), with additional outreach centres in Salford and Leeds. The aim is to provide clinical support, including appropriate provision of haem arginate for severely affected patients with active acute attacks through shared care arrangements with local clinicians.

Acknowledgement

The recommendations for management are based on *Best practice guidelines on clinical management of acute attacks of porphyria and their complications*, developed by the British and Irish Porphyria Network.

References

1 Puy H, Gouya L, Deybach JC. Porphyrias. *Lancet* 2010;375:924–37.
2 Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. *Arch Intern Med* 1993;153:2004–8.
3 Badminton MN, Deybach JC. Treatment of an acute attack of porphyria during pregnancy. *Eur J Neurol* 2006;13:666–72.
4 Marsden JT, Rees DC. A retrospective analysis of outcome of pregnancy in patients with acute porphyria. *J Inherit Metab Dis* 2010;33:591–6.
5 Handschin C, Lin J, Rhee J *et al*. Nutritional regulation of hepatic heme biosynthesis and porphyria through PCG-1α. *Cell* 2005;122:505–12.
6 Hift RJ, Meissner PN. An analysis of 112 acute porphyric attacks in Cape Town, South Africa: evidence that acute intermittent porphyria and variegate porphyria differ in susceptibility and severity. *Medicine* 2005;284:48–60.

Address for correspondence: Dr PE Stein, Department of Medicine, Box 157, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ. Email: penelope.stein@addenbrookes.nhs.uk