ACUTE INTERMITTENT PORPHYRIA IN AN INDIAN MALE ADULT

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SYNOPSIS

We report a case of Acute Intermittent Porphyria (AIP) in a 26-year-old Indian male who presented with severe abdominal pain, mental confusion and hyponatremia after drinking alcohol. His urine turned dark brown after standing for a few hours and was positive for porphobilinogen and porphyrins. The metabolic defect, diagnosis and management of this disorder are briefly discussed.

Acute Intermittent Porphyria (AIP) is a rare disease characterised by episodes of abdominal pain, neuropsychiatric manifestations and increased excretion of porphyrin precursors in the urine. The overall prevalence rate of the disease is 1.5:100,000 of the population although it can be as high as 1:13,000 in Sweden and 1:1,000 in Lapland (1). This condition is very rarely seen in Singapore although one case has been reported in Kuala Lumpur, West Malaysia in 1978 (2). This is a report of a case of AIP in a 26-year-old male tourist from India.

CASE REPORT

A 26-year-old Indian male tourist was admitted to our hospital in August 1983 for severe abdominal pain. He was referred by a private practitioner to the Accident and Emergency Unit, with a note stating that he had passed "port wine" urine. On admission it was not possible to obtain a proper history from him as he was groaning in pain and did not appear to understand English.

Examination showed that he was afebrile with a pulse rate of 78 per minute and BP of 130/70 mm Hg. He was noted to be sweating profusely. There was no odour of alcohol in his breath; jaundice and cutaneous lesions were not detected. His abdomen was

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slightly distended, soft and not tender on palpation. Bowel sounds were absent and rectal examination was normal. He could move all four limbs and deep reflexes were intact. Mentally, he appeared disorientated and confused. He was very restless, stripping himself and standing on his bed. Initially, he was managed as a case of "acute abdomen" with intravenous drip and gastric suction. X-ray of the abdomen showed small bowel distension. He was referred to the surgeon for an opinion. He advised conservative management as there was no evidence of an acute surgical condition. Immediately after admission, the following investigations were done: serum sodium 110 mmol/l, serum potassium 3.2 mmol/l, serum chloride 84 mmol/l, urea 18 mg/dl, serum glucose 98 mg/dl. Further investigations on the next day showed HB 13.8 g%, white cell count 10.500 mm^3 with a differential count of neutrophils 90%, lymphocytes 7%, monocytes 2% and eosinophils 1%. Serum amylase and urine diastase levels were normal. Urine microscopy was normal. He was given 3% hypertonic saline intravenously which raised the serum sodium level to 133 mmol/l. Determination of plasma and urine osmolality after the infusion of sodium chloride showed the values to be 256 mOsm/kg and 585 mOsm/kg water respectively. In spite of correcting his hyponatremia, he remained disorientated and continued to be in pain. He was difficult to nurse and had to be given chlorpromazine to control his disturbed behaviour.

He did not pass urine until the next morning when it was noted that the urine was darker in colour than usual. Examination showed it to be positive for porphobilinogen (Fig 1) and porphyrin. His urine turned dark brown in colour on standing for a few hours (Fig 2). He was treated as a case of AIP and was given intravenous dextrose, glucose drinks and pethidine for his pain. As his condition improved and his pain came under control, he was able to give a more detailed history.

Figure 1 Urine of patient showing pink colouration in the supernatant fluid (acqueous layer) with Watson Schwartz test. Porphobilinogen is not extracted by chloroform which is in the lower layer.

Figure 2 Specimen of patient's urine (right) showing dark brown colour after standing for some hours. Specimen of fresh urine of patient(left) for comparison.

He gave a history of recurrent abdominal pain with 4 episodes of pain over the last 5 years but none was as severe as the present attack. He had never consumed alcohol in India. His present attack occurred on board a passenger ship from India, after he had consumed brandy and 4 cans of beer. He developed abdominal pain, vomiting and constipation during the journey.

His mother has a history of recurrent abdominal pain and had been admitted to hospital several times. The other members of the family are well.

As the patient was a tourist and was in a hurry to return to India, it was not possible to do further investigations on him. He was discharged and advised to abstain from alcohol. He was also given a letter to inform other medical practitioners who might be treating him, the diagnosis of AIP and drugs which should be avoided, especially barbiturates and sulphonamides.

DISCUSSION

Acute intermittent porphyria belongs to the group of metabolic disorders known as the porphyrias in which there is an enzymatic defect in the metabolic pathway leading to the biosynthesis of haem. It is an acute condition and is transmitted as an autosomal dominant trait with a variable degree of penetrance. The first step in the biosynthesis of haem occurs when

glycine combines with succinyl CoA to form delta aminolaevulinic acid (d ALA). This reaction is catalysed by d ALA synthase which can be suppressed by haem or induced by drugs e.g. barbiturates and oral contraceptives. The subsequent steps involve the formation of porphobilinogen (a monopyrrole) which is then converted to a tetrapyrrole, either uroporphyrinogen I or III. It is the III isomer which eventually leads to the formation of haem. In AIP, there is a deficiency of the enzyme uroporphyrinogen I synthase (which in conjunction with uroporphyrinogen cosynthase catalyses the conversion of porphobilinogen (PBG) to uroporphyrinogen III). A block between PBG and uroporphyrinogen results in the accumulation of metabolic precursors such as ALA and PBG, demyelination of nervous tissue and the development of symptoms e.g. pain, neuropathy and psychiatric manifestation.

Stokvis was credited as being the first to report a case of AIP in 1889. His patient was a woman who passed red urine and died after ingesting sulfonmethane (Sulfonal). This disease is perhaps better known as the "royal malady" as it is believed that King George III and other members of the Royal Houses of England and Europe suffered from it (3). Acute intermittent porphyria is important to doctors as it may mimic other conditions because of its diverse manifestations and it has been nicknamed "the little imitator" by Waldenstrom (4).

The onset of symptoms may occur at any age but it occurs most frequently between 20–30 years and rarely before puberty. Females are more frequently affected and this is thought to be due to hormonal changes associated with menstruation, pregnancy and oral contraceptives.

The disease may remain latent throughout life or manifest itself at any time with unpredictable intensity. Attacks are usually precipitated by drugs e.g. barbiturates, oral contraceptives or alcohol, as illustrated by our patient. Other factors include infection, starvation, menstruation and pregnancy.

The most common presenting feature is abdominal pain, occurring in 95% of cases (5). The pain is usually generalised, central and severe, necessitating treatment with pethidine. It is thought to be due to autonomic imbalance in the gut producing areas of spasm and dilatation. The pain is usually accompanied by vomiting and constipation. In general, abdominal tenderness is present to a much lesser degree than the intensity of the pain. In our patient, the absence of guarding made the diagnosis of a surgical acute abdomen less likely. Although our patient was said to have passed "port wine" urine, it was not possible to establish the diagnosis of AIP on admission as he did not pass urine until the next morning. Autonomic disturbance may also result in tachycardia, labile hypertension, postural hypotension, retinal artery spasm and sweating. Profuse sweating was noted in our patient.

Neurological involvement is perhaps the most important feature as death may result from respiratory paralysis. Peripheral neuropathy is predominantly motor, involving initially the proximal muscles, followed by distal muscles of the upper or lower limbs. In severe cases, the patient may become quadriplegic. Other neurological features include grand mal seizures, cranial nerve palsies and urinary retention. Neurological complications did not develop in our patient.

The psychiatric manifestation is also an important feature of the disease as failure to recognise the underlying metabolic disorder has led occasionally to patients incorrectly certified as being insane. Patients exhibit the features of an organic brain syndrome, e.g. confusional state, disorientation and hallucination. Other features include depression, hysteria and anxiety.

Hyponatremia is a well known feature of AIP during the acute attack. The factors involved in its causation include sodium loss in the gut, inappropriate secretion of antidiuretic hormone and renal sodium loss. The main cause of hyponatremia in our patient was most likely inappropriate secretion of anti-diuretic hormone in view of the normal blood urea and blood pressure levels.

DIAGNOSIS

The diagnosis of AIP should be considered when a patient with abdominal pain exhibits neuropsychiatric manifestations. Examination of the urine strongly suggests the diagnosis when the urine changes to a dark red or brown colour on standing for a few hours (Fig 2). The brown colour is due to the polymerization of PBG (which is colourless) to porphyrin and porphobilin which are pigmented. Porphobilinogen is detected by the Watson Schwartz test which is positive when the concentration of PBG is 5–7 mg/l or 2–3 times the upper limit of normal (6). In a patient with latent disease, quantitative assessment of PBG is necessary because it is present in a lower concentration. In prepubertal children, it is preferable to measure the activity of the enzyme uroporphyrinogen I synthase in red blood cells as there may not be an increase in the porphyrin precursors. Acute intermittent porphyria should be differentiated from lead poisoning which has a similar clinical presentation. Although lead was not measured in the blood or urine of our patient, the diagnosis of AIP was considered most likely in view of the family history, recurrent attacks of abdominal pain, relationship to alcohol, presence of hyponatremia and the characteristic increased excretion of porphobilinogen in the urine.

MANAGEMENT

During an acute attack,close observation of the patient is necessary to detect respiratory paralysis which should be treated by artificial ventilation. Respiratory paralysis appears to be more frequently seen in patients who have ingested barbiturates (5). Pain is relieved by pethidine and chlorpromazine is effective in controlling mental symptoms. Hypertension and tachycardia both respond to propranolol. Fits should be controlled by diazepam or paraldehyde and not phenytoin. A high glucose intake is beneficial as it can repress the production of ALA synthase. Intravenous haematin has been used to inhibit ALA synthase by a negative feedback action. Any precipitating factor should be identified and corrected.

After an attack, advice on prophylaxis should be given to the patient. Steps should be taken to ensure

that the diagnosis of AIP in a patient is made known to any medical practitioner in his country or in our parts of the world e.g. by advising the patient to join Medic Alert. Immediate members of the patient's family should be screened for latent disease.

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