ACUTE INTERMITTENT PORPHYRIA: THE FIRST CASE REPORT IN MALAYSIA

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SYNOPSIS

Porphyrias are uncommon disorders of haem metabolism and we report the first documented case of acute intermittent porphyria in Malaysia. The biochemical, clinical features and the management of this order are discussed.

CASE REPORT

S-Z, a 28-year-old Malay housewife from Rawang, presented with a five-day history of colicky abdominal pain, nausea, vomiting and constipation. For these complaints, she was treated with Triglobe (a sulphasalazine-trimethoprim combination) by her doctor for suspected pelvic inflammatory disease. She was anorexic with poor food intake and presented two days later with generalised tonic clonic seizures. There was no past or family history of fits or neurological diseases. She had been previously healthy with two normal pregnancies and fasted yearly during Ramadan without adverse consequences.

On admission, she was drowsy but arousable. She was afebrile with a tachycardia of 100/minute and an elevated blood pressure of 140/95 mmHg. There were no localising neurological signs and the heart and lungs were normal. The abdomen was soft and no abnormality was detected on rectal and vaginal examinations. Investigations showed a haemoglobin level of 13.3 g/l (range 11.5 — 16.5 g/l), white cell count of 10,600/ul (93% neutrophils). The blood urea concentration was 12.9 mmol/l (range 2.3 — 6.8) and the sodium concentration was 131 mmol/l (range 132 — 145). The biochemical liver function test, serum calcium, phosphorous, magnesium, fasting blood sugar, fasting triglycerides and cholesterol levels were within normal limits. Urinalysis revealed pyuria with no growth on culture. The ECG showed sinus tachycardia of 100/minute and the chest X-ray was normal. CSF pressure was 20 cm. water with normal biochemistry and cell count. The EEG showed diffuse abnormality with focal slow waves over the right temporal and parietal regions. The computerised tomographic examination of the brain was normal.

The patient was treated with phenytoin 300 mg. for her convulsions and propranolol and hydrochlorothiazide for the hypertension. There was no past or family history of hypertension and the urine hydroxymethyl mandelic acid and normetanephrine levels were not raised. She showed signs of confusion, disorientation and hallucinations even though her seizures were well controlled. She was generally weak and developed urinary incontinence with retention. A catheterised specimen of urine was noted to be dark red. Nine days after her admission, the patient developed rapidly progressive generalised paresis and respiratory distress requiring ventilatory support.

Investigations at that time showed a normal haemoglobin level, leucocytosis of 28,600/ul (with 99% neutrophils), severe hyponatremia (serum sodium concentration of 105 mmol/l) and hypochloremia (serum chloride concentration of 74 mmol/l). The blood gases showed respiratory alkalosis with mild hypoxemia (p02 = 10.4 kPa, pCO2 = 3.4 kPa). The ECG and chest X-ray were normal. In view of the complex presentation of abdominal pain, persistent tachycardia, hypertension, neurological signs, dark red urine and severe hyponatremia acute intermittent porphyria was suspected. Estimation of urine porphobilinogen (PBG), porphyrins (1) and urobilinogen (2) and faecal porphyrins were carried out. The results are shown in the table. Urine PBG was raised at 102 umol/1 and urine porphyrins and urobilinogen were present while faecal porphyrins were absent. The three time mean of urine PBG in ten healthy local subjects was 4 umol/l. Lead poisoning was excluded by the absence of punctuate basophilia in the peripheral blood film and normal blood and urine lead levels.

All offending drugs, e.g., phenytoin, were withdrawn and electrolyte imbalances corrected. The patient was given a high carbohydrate diet (about 400 gm. per day) and with this the urine PBG levels decreased to 35 umo/1. Subsequently she could not be weaned off the respirator and developed adult respiratory distress syndrome. She succumbed five weeks after admission. No consent for post mortem was granted.

The urine of her husband, son (7 years) and daughter (3 years) were also screened for PBG but only the son showed a positive test. There was no history of foreign ancestry in the family.

DISCUSSION

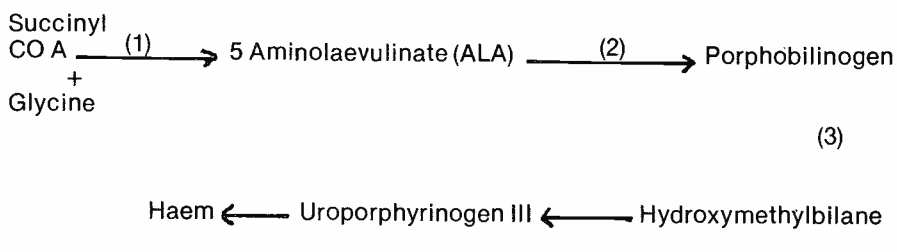
In 1889, Stovkis reported the first case of acute intermittent porphyria (AIP) following sulphonamide ingestion (3). Porphyrias can be classified into hepatic or erythropoietic porphyrias (4). AIP is the commonest form of hepatic porphyria and is due to the partial deficiency of uroporphyrinogen I synthetase activity (figure 1) in hepatocytes and other tissues with associated increase in alanine laevulinic acid (ALA) synthetase activity. The biochemical defect results in an increase in the production of ALA and PBG which are excreted mainly in the urine, the latter polymerising to form porphyrins when exposed to sunlight. The diagnostic features of AIP consists of increased levels of ALA and PBG in the urine with absence of faecal porphyrins which are present in other forms of hepatic porphyrias.

TABLE: RESULTS OF URINARY INVESTIGATIONS

Days after diagnosis*	1	5	8	9	14
Quantitative PBG (umol/1)**	102	24	41	35	21
Qualitative PBG	+ +	+	+	+	NA***
Porphyrin	+ +	+	trace	+	NA***
Urobilinogen***	+	+	+	+	NA***

* High carbohydrate diet was instiuted on day 1
** Mean of PBG from 10 healthy subjects = 1.4 ± 0.5 umol/l
*** NA = not analysed
**** Confirmed by Schlesinger's test (2)

FIGURE 1: THE PATHWAY OF HAEM BIOSYNETHESIS AND THE SITE OF ENZYMATIC BLOCK IN AIP



(1): ALA synthetase
(2): ALA Dehydratase
(3): Uroporphyrinogen I synthetase

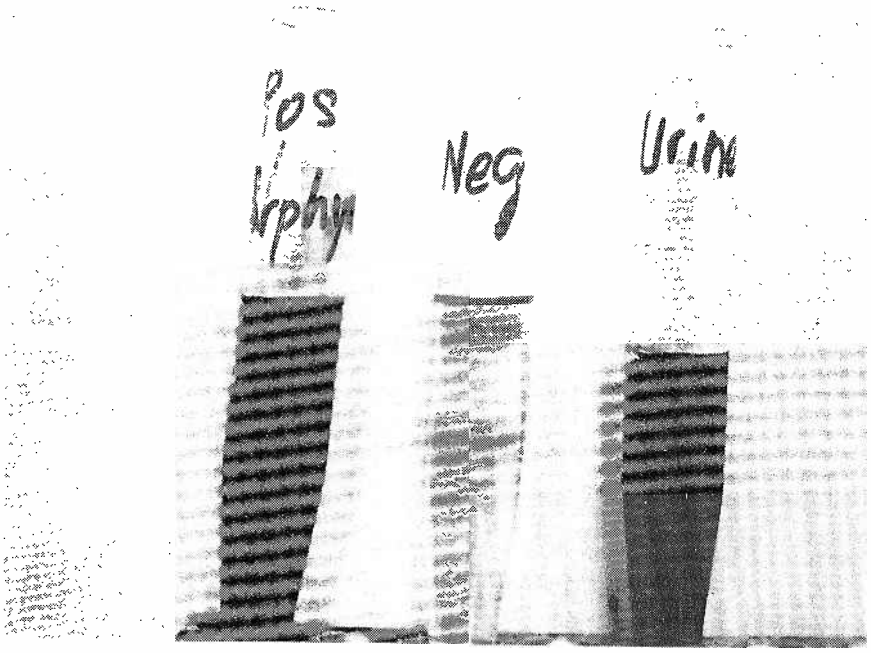
AIP is inherited as an autosomal dominant trait (5). However, only 1 in 3 will suffer from the acute attack (6). The gene frequency is estimated to be between 1 in 10,000 and 1 in 50,000 in the West and is unknown in South East Asia. It is commoner in females than in males with the usual age of presentation being in the third decade for females and fourth decade for males. The acute attack can be precipitated by (i) change in steroidal hormone metabolism, e.g., in pregnancy and menstruation , (ii) infection and (iii) starvation (7). In this case, the attack was precipitated most probably by the combination of both Triglobe and a low food intake and accentuated by phenytoin.

Our patient had some of the classical features of AIP such as abdominal pain (in 95% of Stein's cases (8), nausea and vomiting (in 43% of cases) and constipation (in 48% of cases). Seizures occurred in 8 out of 40 patients of the same series and mental confusion and hallucinations in 16 of the 40 patients. All forms of impaired cranial and peripheral nerve function may be found in AIP. Quadriparesis (as observed in our patient) was present in 11 of 35 patients (Stein's series) and only 3 of these progressed to respiratory paralysis. Our patient also showed signs of autonomic neuropathy such as persistent tachycardia (80% of cases), hypertension (36% of cases) and urinary retention (12% of cases).

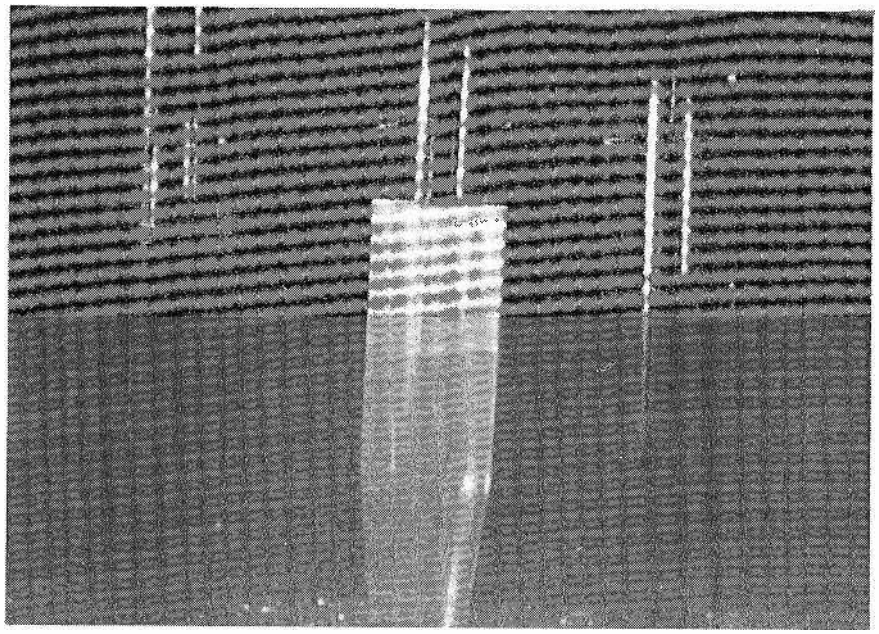
S-Z, (our patient), showed hyponatremia with inappropriately normal urine sodium concentration. This suggests an inappropriate antidiuretic hormone secretion and/or a defect in tubular handling of sodium. Hypomagnesemia, hypercholestrolemia and an abnormal glucose tolerance, and an increased thyroxine concentration (not measured in this patient) may also occur but these changes were not observed in our patient. The biochemical liver function test is usually normal except for an increase in bromosulpthalein retention (9). We postulate that the presence of urobilinogen in the urine in our patient could be related to the decrease in hepatic bromosulpthalein clearance observed in AIP. In Stein's series, the majority of patients had normal brain scans and normal CSF cytology and biochemistry. The EEG usually showed diffuse non-specific slow waves. Like in our patient, two cases showed focal abnormality and these reverted to normality after recovery.

The most important aspect of management is to withhold all incompatible drugs (10), and correct electrolyte and fluid imbalances. The institutioin of a high carbohydrate intake (400 gm. daily) decreases ALA and PBG production (11). Watson has shown that intravenous haematin aborts the attack by suppressing ALA synthetase activity but the drug is not available locally. Since the disease is transmitted in an autosomal manner, all siblings and relatives should be screened for the presence of urinary PBG. Latent cases c be detected by measuring urinary PBG excretion after reduced calorie intake (12) and/or the quantitation of leucocyte ALA synthetase and erythrocyte uroporphyrinogen I synthetase activities (13). The patient's son has been given a medic alert and a list of drugs to avoid.

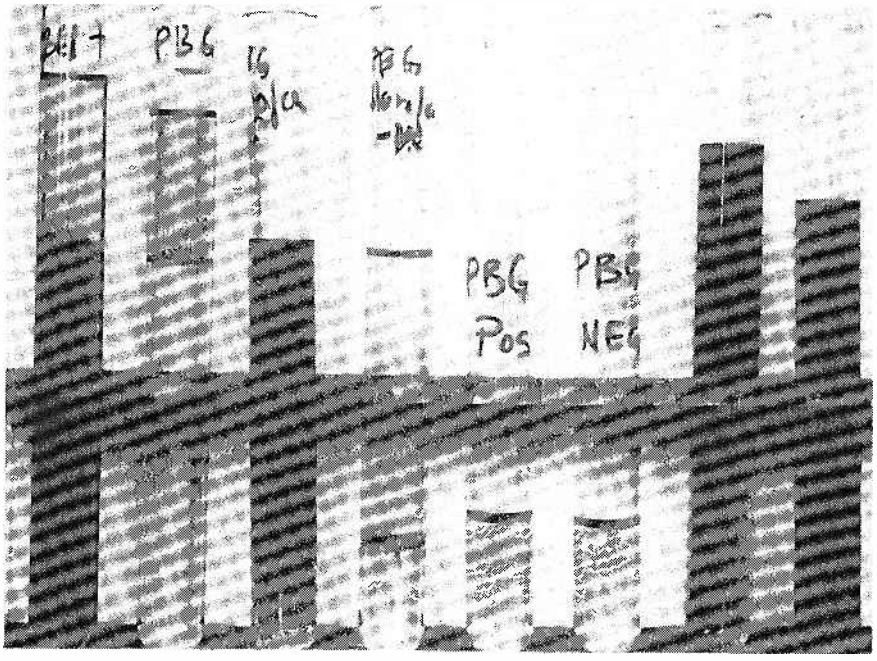
AIP, though rare, does occur in Malaysia and must be included in the differential diagnosis of patients with the clinical features of acute abdominal pain, neurological signs, persistent tachycardia, labile blood pressure and dark red urine. The simple urinary PBG screening test should be made routinely available in all laboratories.



(A): Shows from the left, tube 1 of patient's urine (bottom layer) extracted with acetic acid/amyl alcohol mixture (top layer), tube 2 a negative control similarly extracted, tube 3 of patient's urine after exposure to sunlight.



(B): Shows tubes from figure A when exposed to UV light showing red fluorescence of porphyrin in the urine (tube 3) and in the acetic acid/amyl alcohol layer (tube 1) and no red fluorescence was detected in the extracted negative control (tube 2).



(C): Shows pink colour remainded in aqueous layer after reacting the urine with Erhlich's reagent and extracting it with butanol (bottom layer, tube 1 from left) and chloroform (top layer, tube 3). Tube 2 and 4 were negative controls similarly treated. Tube 5 showed a tint of pink after passing the positive urine through an ion exchange column and reacting with Erhlich's reagent. The eluate was measured at wavelength of 555 nm. Tube 6 was a negative control similarly treated. After the reaction between urobilinogen positive urine and Erhlich's reagents, the less polar complex was extracted into butanol (top layer, tube 7) and choloroform (bottom layer, tube 8) layers.

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