ACUTE INTERMITTENT PORPHYRIA — A CASE REPORT

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SYNOPSIS

A case of acute intermittent porphyria presenting with acute abdominal pain, hypertension, tachycardia and fits is described. The fundamental defect in the heme biosynthetic pathyway is outlined and the chemical diagnosis and treatment is discussed.

INTRODUCTION

Acute intermittent porphyria (AIP) is an inborn error of metabolism characterised by excessive excretion of porphyrin precursors and involves variable patterns of neurologic and metabolic disturbances. Stokvis (1889) described the first recorded case of AIP in a woman who passed red urine. In 1931 it was discovered that the urine of AIP patients contained porphobilinogen and it was only recently in the early 1970's that the fundamental defect was traced to the reduction in the enzyme uroporphyrinogen I synthetase associated with a marked increase of hepatic α-aminolaevulenic acid synthetase — the first and rate limiting enzyme in the porphyrin biosynthetic pathway. The disease occurs in all races. The prevalence in Sweden is 1 : 13,000, Ireland 1 : 8,000 and Western Australia 1 : 100,000. The manifest disease is significantly more common in women in all the major series. The mode of inheritance is autosomal dominant.

CASE REPORT

A 23 year old woman presented with a history of colicky episodic abdominal pain three weeks prior to admission. Pain was described as severe and progressive. There was associated vomiting but no diarrhoea, haematuria or dysuria. She had been married for nine months and was amenorrhoeic for twelve weeks. There was no vaginal discharge or spotting and there were no fainting episodes. She was admitted to two hospitals during the duration of her illness but her condition continued to deteriorate and no diagnosis was arrived at. On the day of admission to the General Hospital, Kuala Lumpur she developed generalised convulsions

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which lasted for about three minutes following which she became violent and aggressive. There was a reddish discolouration of the urine over the past few days and she had constipation for ten days.

On admission she was conscious but violent and disorientated. The blood pressure was 160/120 mm Hg. and the pulse rate was 110/min. and regular. The temperature was normal. There was no neck stiffness and Kerning's sign was negative. She moved all four limbs well. The biceps, triceps and knee jerks were normal but the supinator and ankle jerks were absent. The plantar reflex was normal. The respiratory system, skin and abdomen were normal.

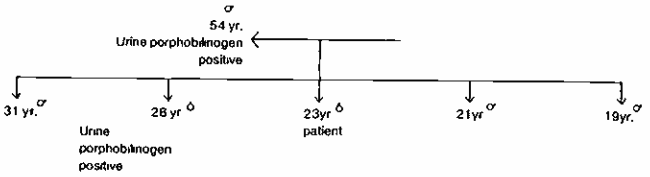
The patient's urine stained the bed-sheet red. The window still test and the Watson Schawartz test for porphobilinogen were positive. Blood urea on admission was 42 mgm%, serum sodium 132 meg/L, serum potassium 4.4 meq/L, serum chloride 95 meq/L. Repeated samples of serum sodium and chloride showed hyponatremia and hypochloraemia.

Date	11.2.77	13.2.77	23.2.77	11.3.77
Sodium	100 meq/L	120 meq/L	127 meq/L	128 meq/L
Chloride	67 meq/L	66 meq/L	100 meq/L	93 meq/L

Liver function tests showed: Total bilirubin 1.0 mgm%, Alkaline phosphatase 5.5 KA units, zinc sulphate turbidity (Kunkel) 10 units, Total proteins 4.8 gm%, Albumin 2.3 gm%, Globulin 2.5 gm%, A/G ratio 0.9, SGPT 20 RF units. Urine pregnancy test was positive. 24-hour urine sodium excretion was 7 meq. Urine analysis for lead showed 0.02 mgm of lead per litre. Arsenic was negative in both nail clippings and urine specimen. Cerebro-spinal fluid examination was normal with proteins 21 mgm%, sugar 75 mgm%, chloride 114 meq/L, and globulin negative.

The patient had a stormy course in hospital with recurrent seizures which were controlled with paraldehyde and diazepam. She developed flaccid paralysis with bilateral wrist and foot drop and aphonia. There was labile hypertension and tachycardia which were controlled with oxyprenolol. She aborted spontaneously approximately seven weeks after admission but there was no improvement in her clinical status. Urine porphobilinogen was negative on 27.4.77. Four months after the onset of her illness she recovered some motor power and was able to talk.

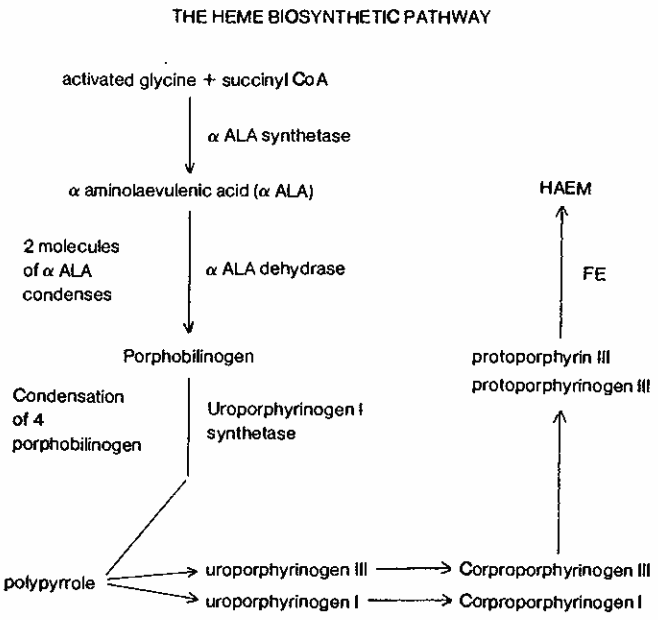
In the family history it was found that her father, 54 years old suffered recurrent abdominal pain at the age of 27 years. This complaint occurred on and off for five years and he was hospitalised once in the General Hospital, KualaLumpur for three months but no diagnosis was made. An elder sister, 28 years old also had recurrent abdominal pain for about one year at the age of 25 years. The family was screened for urine porphobilinogen and it was positive in both the father and sister. The family chart is illustrated below:



DISCUSSION

An acute attack of AIP varies considerably in its clinical presentation and patients may be referred to an internist, surgeon, neurologist, psychiatrist or gynaecologist. A high level of clinical suspicion is necessary in order not to miss the diagnosis which is based on relatively simple laboratory examination for porphobilinogen. An increased urinary excretion of porphobilinogen in the absence of lead or arsenic poisoning points towards a diagnosis of acute intermittent porphyria. It is probable that the father and sister had undiagnosed attacks of AIP when they suffered abdominal pain.

A brief review of the heme biosynthetic pathway is outlined in order to explain the fundamental defect in AIP.



α Aminolaevulenic acid synthetase is the first and also the rate limiting enzyme in the pathway. In AIP there is reduction in the enzyme uroporphyrinogen I synthetase which catalyses the condensation of 4 molecules of porphobilinogen to form polypyrroles. Diminished haem synthesis causes induction of the rate limiting enzyme-α ALA synthetase via a biofeedback mechanism and

thus results in high levels of porphobilinogen in the blood and urine.

AIP is a genetic disease that remains latent until acted upon by superimposed factors. The precipitating factors in AIP include: 1) drugs, 2) certain steriods, 3) starvation and 4) infection. Drugs known to precipitate acute attacks of AIP include barbiturates, griseofulvin, sulphonamides, chlorodiazepoxide, glutethimide, meprobamate, diphenylhydantoin, methosuximide, pyrazolone compounds, imipramine, ergot preparations, tolbutamide etc. Steroids and hormones comprise the second group of factors. The manifestations of the disease occurring often after puberty and the female preponderance of clinically manifest disease in all major series suggest the role of the female hormone in actiating the disease. Some women regularly have attacks just before menstruation the disease has been reported to become active during pregnancy.

The clinical manifestations of the disease can be explained by lesions in various areas of the nervous system. Abdominal pain is the initial symptom in 85% of acute attacks and it has been demonstrated to be due to autonomic neuropathy producing an imbalance in gut innervation with resultant areas of spasm and dilatation. Pain in the back and extremities are common. Motor paralysis may be symmetrical or localised and occasionally a devastating complete flaccid paralysis of all four extremities may occur. Cranial nerves may be involved and there may be aphonia, respiratory paralysis and dysphagia. Other neurological manifestations include peripheral psychiatric disturbances and seizures. The patient reported here demonstrated severe neurological involvement with complete flaccid paralysis of all four extremities, aphonia and seizures.

Hyponatremia may be present and is mainly due to gastro-intestinal loss through vomiting but some of these patients manifest inappropriate anti-diuretic hormone secretion while in others subtle renal lesions may cause sodium loss and hypovolaemia which stimulate prolonged anti-diuretic hormone secretion. The metabolic disturbance in this patient was hyponatremia and there was tachycardia and labile hypertension at the time of admission and during her stay in the ward.

Porphobilinogen in the urine can be demonstrated by the window sill test or the more sophisticated Watson Shwartz test. A more sensitive method for quantitative estimattion of porphobilinogen is available and can detact levels below which the Watson Shwartz test becomes negative. Other conditions that may cause increased serum and urinary porphobilinogen are lead and arsenic poisoning.

All cases of AIP in acute attacks will excrete increased porphobilinogen in the urine. However some asymptomatic cases will excrete normal amounts of porphobilinogen in the urine which means that measurement of porphobilinogen is not infallible in detecting the disease in asymptomatic cases. A simple method has been devised for the estimation of uroporphyrinogen I synthetase level in red blood cells and this is a more reliable and specific test.

Treatment can be discussed under three aspects 1) prophylaxis, 2) treatment of symptoms and complications and 3) attempts to reverse fundamental defects. Detection of the disease in asymptomatic patients and avoidance of the precipitating factors can be life saving. Chlorpromazine is useful for control of abdominal pain through the autonomic inhibition properties. Beta-blockers are valuable in treating persistent sinus tachycardia and diazepam or paraldehyde are useful to control seizures.

Two approaches are available to reverse the fundamental disease process. This involves the use of high carbohydrate diet and haematin. A high carbohydrate diet can lower porphyrin precursor excretion by the action of glucose in blocking the induction of hepatic α-aminolaevulenic acid synthetase. The clinical response however is variable ranging from spectacular recovery to little or no effect. 450 gm to 500 gm of carbohydrate is given a day where possible. Intravenous haematin has been shown to suppress hepatic α aminolaevulenic acid synthetase production probably via a biofeedback mechanism.

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