

Case Report

A 11-Year-Old Girl with Acute Intermittent Porphyria (AIP)

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INTRODUCTION

Porphyrias are inherited disorders due to enzymatic defects in the heme-synthesis, with accumulation of porphyrins. All forms may arise in childhood and are often under-diagnosed^[1]. Based on the site of excess production of porphyrins, patients are classified as hepatic and erythropoietic or clinically as acute or non-acute. Acute cases present mainly with neuro-psychiatric symptoms and non-acute present mainly with skin involvement. The majority of cases are autosomal dominant with variable penetrance.

Researchers have pointed out that the disorder affected some members of the Houses of Stuart, Hanover and Prussia^[2,3], and was directly responsible for two major crises. The first was the Regency crises in 1785 when George III had an acute attack. The second was the deaths of Princess Charlotte and the baby during childbirth in 1817 due to an acute attack of porphyria. Charlotte and the baby represented the next two successions to the throne.

Due to their diverse manifestations, porphyrias should be considered in the differential diagnosis in a patient presenting with multi-system involvement.

Case presentation:

An 11-year-old girl, developmentally and neurologically handicapped, developed recurrent episodes of lethargy, poor appetite, abdominal pain and vomiting over a four year period. She had experienced red-color urine intermittently for the past one year. She was born at term, weighing 2.6 kg and did not require special care during the newborn period. When she was three months old, she was diagnosed as a case of Tetralogy of Fallot and was operated twice at the age of five months and two years, respectively. During the first operation, she suffered a cardiac arrest and since then, she has developed seizures, which were

partially controlled with sodium valproate and tegretol. In addition, she had recurrent attacks of abdominal pain and lethargy associated with vomiting which required five hospital admissions. During the second admission, an appendectomy was done. Both unrelated parents are well. Four other siblings were reported in good health.

At present, she is in a special school for educationally challenged children. Her maturity Gesell developmental test goes with six years. The sex maturity rating (Tanner) is in stage III of breast development.

On admission, her weight was at the 10th centile and the height at the 50th centile. She was dehydrated but alert with a blood pressure of 98/55 mmHg. Central nervous system examination showed intact cranial nerves, with mild dysarthria. Limb tone was normal and the tendon reflexes were not increased. A median scar of sternotomy was present and a soft systolic murmur was heard at the left sternal border. The abdomen was soft with no hepato-splenomegaly. The examination of skin was normal.

Investigations revealed Hb 12.7g/dl; Wbc $3.1 \times 10^9/L$; platelets $118 \times 10^9/L$; reticulocytes 0.5%; ESR 6 mm/h. Serum analyses values were as follows: glucose 5mmol/l; Na 118 mmol/l; K 4.19 mmol/l; urea 8.6 mmol/l; bicarbonate 22 mmol/l; aspartate transaminase 765 IU/l; alanine transaminase 671 IU/l. Blood lead, ammonia and G-6-PD levels were normal. Hepatitis antibodies were negative. Porphobilinogen (PBG) deaminase was 190 u/l [N: 85-165]. Urine analysis showed protein -ve; Wbc 3-5/hpf; Rbc 1-2/hpf. Urine high performance liquid chromatography showed Aminolevulinic acid (ALA) 190umol/l (3.13mmol/l); Creatinine 4.17 mmol/l. ALA/Creatinine ratio was 45.62 umol/mmol (N:<4.30).

She continued to have abdominal pain and she developed bilious vomiting. She was given IV

fluids with 10% dextrose, sodium valproate, and vegabactrim. The tegretol was discontinued. On day four, she developed myoclonic jerks and mild hypertension (135/88 mmHg) which were controlled with Diazepam. In addition, she had persistent hyponatremia, which was treated with fluid restriction and half-normal saline. Four weeks later, she developed abdominal pain, abnormal behavior and hemiparesis. Sodium valproate was stopped and eight weeks later, she made a full recovery. Urine analysis was repeated in the interval period and was positive for ALA/PBG.

DISCUSSION

The clinical features in this case were suggestive of multi-system disease. A normal blood lead level ruled out lead poisoning. Her past history was significant. She had recurrent abdominal pain, seizures, and behavioral changes and was passing purple-red urine, which were all in favor of AIP. Her urine was purple-red due to conversion of urine PBG to porphobilin, which is accelerated by light, heat, or acid^[5]. She also had non-specific alterations in the liver function tests and persistent hyponatremia, probably secondary to hypothalamic dysfunction giving rise to the syndrome of inappropriate antidiuretic hormone release (SIADH). Hypothalamic uptake of labeled ALA is greater than in any other area of the brain. This can explain the occurrence of SIADH in AIP^[6]. After her cardiac arrest during surgery, she developed seizures, which were poorly controlled. The anti-convulsants and the raised ALA produced during the attacks of AIP are probably responsible for their poor control. Injected ALA into the brains of rats caused behavior changes, seizures and duodenal contraction, etc^[7,8].

In our patient, the PBG deaminase in RBCs was reported to be normal. Some patients with AIP who are clinically affected displayed no evidence of PBG deaminase deficiency in erythrocytes^[9,10]. The clinical and biochemical abnormalities found in these patients are due to deficiency of PBG deaminase in the liver. In these cases, decreased activity of PBG deaminase may be detected in cultured fibroblasts^[11] or in mitogen-stimulated lymphocytes^[12].

CONCLUSION

Acute intermittent porphyria is an autosomal dominant disorder with more than 90 mutations reported in the PBG deaminase gene. Due to accumulation of ALA and PBG, there is neurological dysfunction (autonomic, peripheral and central nervous system) often associated with psychosis^[13]. The skin sensitivity displayed in other

porphyrias, however, is not seen in this disorder. The majority of people with AIP remain clinically normal. Usually an acute attack begins with abdominal pain, vomiting constipation, muscle weakness, mental symptoms and rarely respiratory failure. The primary genetic defect in AIP is due to deficiency PBG deaminase, which leads to an accumulation of ALA and PBG. It rarely presents before puberty but reduced food intake, infection, steroids, surgery and certain drugs^[14] may precipitate an attack (Table 1). The attacks decrease in women after menopause. Sex steroids induce the synthesis of hepatic ALA synthetase with excess production of ALA and PBG^[15]. Inhibition of ovulation with long-acting agonists of luteinizing-hormone-releasing hormone has been shown to greatly reduce the incidence of perimenstrual attacks of AIP^[16].

The diagnosis is made based on the history, demonstration of high concentration of ALA and PBG in urine, PBG deaminase assay in the erythrocytes, in cultured skin fibroblasts or mitogen stimulated lymphocytes. Elevated levels of ALA and PBG may also be seen in Hereditary coproporphyria (HCP) and Variegate porphyria (VP). Urine and stools porphyrins assays usually differentiate these conditions.

The management is supportive. It includes a high carbohydrate intake, IV dextrose, and propranolol for tachycardia and hypertension^[17], as well as the avoidance of harmful drugs, alcohol, fasting and prompt treatment of infections.

Psychiatric manifestations are usually controlled with chlorpromazine. Intravenous hematin infusion for a short term appears to be of benefit as it decreases the activity of enzyme ALA synthetase, the first step in the heme synthesis and stops the excessive production of ALA^[18]. The above measures should be used early in the attack before any nervous or respiratory complications develop. The course of an acute attack is variable. It may last for a few days to months and in the majority of cases, there is a slow return to normal functions.

Table 1

Some of the drugs that aggravate porphyria

Barbiturates	Alkylating agents
Carbamazepine	Hydralazine
Chlorpropamide	Methyldopa
Diphenylhydantoin	Clonidine
Trimethadione	Ketamine
Valproic acid	Phenoxybenzamine
Sulfonamides	Theophylline
Erythromycin	Spirolactone
Nalidixic acid	Chloroquine
Rifampicin	Synthetic estrogens
Pyrazinamide	Progestins

REFERENCES

1. Elder GH. Recent advances in the identification of enzymes deficiencies in porphyrias. *Br J Dermatology* 1983; 108:729.
2. Macalpine I, Hunter. The insanity of King George III: a classical case of porphyria. *Br J Med* 1966; 1:1.
3. Macalpine I, Hunter R, Remington C. Porphyria in the Royal Houses of Stuart, Hanover and Prussia: a follow-up study of George 3d's illness. *Br Med J* 1968; 1:17.
4. Loftus LS, Arnold WN. Vincent Van Gogh's illness: Acute intermittent porphyria? *B M J* 1991; 303:1589-1591.
5. Day RS, Eales L, Disler PB. Porphyrias and the kidney. *Nephron* 1981; 28:261.
6. Hellman ES, Schudy DP, Bartter FC. Abnormal electrolyte and water metabolism in acute intermittent porphyria. *Am J Med* 1962; 32:734.
7. Shanley BC, Neathing AC, Percy VA, Carstens M. Neurochemical aspects of porphyria: Studies on the possible neurotoxicity of delta aminolevulinic acid. *S Afr J Lab Clin Med* 1975; 49:576.
8. Pierach CA, Edward PS. Neurotoxicity of delta-aminolevulinic acid and porphobilinogen. *Exp Neurology* 1978; 62:810
9. Mustajoki P. Normal erythrocyte uroporphyrinogen I synthetase in a kindred with acute intermittent porphyria. *Ann Intern Med* 1981; 95:162.
10. Wilson JHP, de Rooij FWM, te Velde K. Acute intermittent porphyria in the Netherlands: Heterogeneity of the enzyme porphobilinogen deaminase. *Neth J Med* 1986; 29:393.
11. Sassa S, Solish G, Levere RD, Kappas A. Studies in porphyria: Expression of the gene defect of acute intermittent porphyria in cultured human skin fibroblasts and amniotic cells : prenatal diagnosis of the porphyric trait. *J Exp Med* 1975; 142:722.
12. Sassa S, Zalar GL, Kappas A. Studies in porphyria VII. Induction of uroporphyrinogen I synthase and expression of the gene defect of acute intermittent porphyria in mitogen-stimulated human lymphocytes. *J Clin Invest* 1978; 61:499.
13. Tishler PV, Woodward B, Oconnor J, Holdbrook DA, Seidman LJ, Hallet M, Knighton DJ. High prevalence of intermittent acute porphyria in a psychiatric patient population. *Am J Psychiatry* 1985; 142:1430.
14. Blekkenhorst GH, Cook ES, Eales L. Drug safety in porphyrias. *Lancet* 1980; 1:1367.
15. McColl KEL, Wallace AM, Moore MR, Thomson GG, Goldber A. Alterations in heme biosynthesis during the human menstrual cycle: Studies in normal subjects and patients with latent and active acute intermittent porohyria. *Cli Sci* 1982; 63:183.
16. Kappas A. Prevention of cyclical attacks of acute intermittent porphyria with a long-acting agonist of luteinizing hormone releasing hormone. *N Eng J Med* 1984; 311:643.
17. Beattie AD, Moore MR, Goldberg A, Ward RL. Acute intermittent porphyria: Response of tachycardia and hypertension to propranolol. *Br Med J* 1973; 3:257.