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Acute intermittent porphyria in childhood

A neglected diagnosis?

It has been stated frequently that acute intermittent porphyria does not occur before puberty and most authorities agree that it is very rare in childhood (Barltrop, 1964; Chisolm, 1964, 1969; Gupta, Singh, and Prabhaker, 1967). In reviewing previously published cases the question arose, is it the disease or merely the diagnosis that is so rare in childhood?

The following case report illustrates several of the classical signs and symptoms.

Case report

A male was born by normal delivery after a normal pregnancy, with a birthweight of 2·44 kg. There was no previous history of fits or of any serious illness. His skin was normal. He attended a normal school but was in the lower educational stream. He was known to eat paper, pencils, and cellophane.

The family was of Anglo-Saxon origin. A maternal uncle had had fits during childhood only, and one maternal aunt had suffered from a cerebral incident at the age of 38 years. In neither parent was there a history of any noteworthy illness. There was one younger sister who was healthy.

He was first admitted at the age of 9 years 9 months to the surgical unit at Hillingdon Hospital in September 1969. 3 days previously he had vomited and then complained of abdominal pain situated just to the right of the umbilicus. On admission his temperature was 37·4 °C. A diagnosis of mesenteric adenitis was made and he was sent home 5 days later.

At the age of 11 years 2 months, on 19 February 1971, he was readmitted with a history of constipation for one week, central abdominal pain for 4 days, and of suddenly falling down with a generalized convulsion on the afternoon of admission.

On admission his weight was 54·4 kg (well above the 97th centile). He was afebrile and had no neck stiffness. The abdomen showed no rigidity, but he complained of mild generalized tenderness. Clinical examination was otherwise normal.

During the 4 hours after admission he had four further generalized convulsions with varying signs in the CNS, leaving him with a marked left facial nerve palsy. Blood pressure varied between 145/110 and 140/95 mmHg. Pulse rate was 120/min. CSF was clear, colourless, with protein 17 mg/100 ml, no excess globulin, glucose 80 mg/100 ml, and no increase in cells. Plasma sodium at this stage was 128 mEq/l. and chloride 91 mEq/l. Diazepam 10 mg was given intramuscularly, followed by phenytoin 50 mg and phenobarbitone 30 mg 8-hourly.

It had now become obvious that the diagnosis was other than uncomplicated epilepsy. Urine showed no abnormality on microscopy, though it was noted to be pink in colour. Blood glucose level was 143 mg/100 ml and urea 60 mg/100 ml. Skull *x*-ray was normal. Medication with phenobarbitone and phenytoin was continued and after a further 12 hours the fits abated. As the blood pressure readings remained raised, pentolinium 1 mg was given intramuscularly on 22 February but with no effect. An intravenous pyelogram showed normal renal outlines and function.

Four days after admission, however, repeat plasma electrolyte estimation showed sodium 110 mEq/l., potassium 3·5 mEq, chloride 78 mEq, and bicarbonate 22 mEq, and urea 30 mg/100 ml. Normal sodium chloride solution by continuous intravenous infusion was given along with dexamethasone 4 mg intramuscularly, 8-hourly.

On 23 February it was noticed in the laboratory that the urine had turned dark red on standing and gave a strongly positive test for porphobilinogen. No porphyrins were detected at this time. Accordingly, phenobarbitone administration was stopped and chlorpromazine 25 mg intramuscularly substituted. This had no effect on the electrolyte disturbance and little effect on the convulsions which had now returned. The chlorpromazine was subsequently reduced to 12·5 mg 6-hourly and was finally stopped as the child became progressively less responsive and completely comatose on 24 February.

On 25 February it was decided to chelate with sodium calcium versonate, which was continued for a total of 5 days. Before starting this, a sample was taken for blood lead estimation which was later reported as 28 μg/100 ml.

On 26 February his condition slightly improved. On the following day he was confused but talking, and the next day was eating normally. On 1 March he had repeated hallucinations which were relieved by chlorpromazine. CNS signs persisted and on 4 March he was still ataxic with extensor plantar responses. Porphyrins appeared in the urine for the first time on 27 February and persisted thereafter. He was discharged well on 9 March. Further progress has been satisfactory with no residual CNS signs. EEG showed minor changes consistent with a diagnosis of epilepsy. When last seen on 30 March 1973, he was well, with blood pressure 125/70 mmHg. Urine contained both excess

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porphobilinogen and excess porphyrins. Blood lead level was 17 μg/100 ml.

The father also excretes porphobilinogen in his urine, though he has never had any symptoms that could be related to the condition. The child's younger sister shows no porphobilinogen and no porphyrins in the urine.

Discussion

Apart from the age of the patient, one of the most interesting facts of this case is that the child was completely comatose for 3 days and yet made a full recovery. This has not often been reported, and one is tempted to attribute this not to the withdrawal of phenobarbitone (36 hours before the child became comatose), but to the administration of a chelating agent, namely, sodium calcium versonate. This treatment has been reported elsewhere (Peters, Eichman, and Reese, 1958), the rationale having been originally that the abnormal pyrrole metabolism reflected an attempt to chelate unwanted copper and zinc, the accumulation of which was the primary cause of the disease. Present theories give no support to this concept. However, the fact remains that the treatment was apparently effective, and in a potentially lethal situation clinical trials are justified to refute its success.

The diagnosis, symptoms, biochemistry, and treatment of the conditions have been more than adequately reviewed elsewhere (Aldrich, Labbe, and Talman, 1955; Peters *et al.*, 1958; Goldberg and Rimington, 1962; Dogramaci, 1964; Tschudy *et al.*, 1965; Ridley, Hierons, and Cavanagh, 1968; Ridley, 1969; Salokannel and Rhen, 1969; International Conference, 1971).

Apart from the hexachlorobenzene tragedy in Turkey, involving almost 4500 children under the age of 16 years (Dogramaci, 1964), 37 previously published paediatric cases were traced and a few facts emerged.

As in adults, there is a female preponderance. In many of the cases of which we have details there was at least one previous episode before diagnosis, most commonly abdominal pain. An unexpectedly high number of cases presented at the time of diagnosis with central or peripheral nervous system involvement. Only a few patients had recognized psychiatric disturbance either during or between attacks; a low incidence compared with series of adult cases.

In spite of the fact that either pathological porphyrins, porphobilinogen, or increased δ-aminolaevulinic acid was found in the urine of all patients, several children in the series were never noticed to have a coloured urine (Mays, 1967). One child was desperately ill for 3 months, but only produced dark red urine one week before death (Monro, 1907). In some instances this may have been accounted for by not allowing sufficient time for the urine to change colour. However, Peters *et al.* (1958) also commented that though specimens of urine known to contain porphobilinogen were exposed to sunlight and acidified, no colour change was noticed in some cases.

These findings are disturbing. This is a disease in children which is potentially fatal and can present with minimal symptomatology, but may not be diagnosed until the final fatal attack.

Thus, a high degree of suspicion among both paediatricians and paediatric surgeons appears to be the only way to improve the diagnosis rate.

Summary

A boy aged 11 years with acute intermittent porphyria is reported. He presented with abdominal pain and generalized convulsions, and was found to have hypertension, hyponatraemia, and a red coloured urine containing porphobilinogen. In spite of being comatose for 3 days, the child made a full recovery, which may have been attributable to his treatment with sodium calcium versonate.

37 paediatric cases were found in reviewing published reports on acute intermittent porphyria. Though this disease is thought to be very rare in childhood, mild cases presenting merely with abdominal pain may escape diagnosis. A port-wine coloured urine was not always noticed in proven cases that have been published, possibly because the urine was not left standing long enough in some instances. In view of the potentially fatal outcome of a severe attack, a higher index of suspicion is essential in paediatric practice.

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Acute intermittent porphyria, hypercholesterolaemia, and renal impairment

Acute intermittent porphyria is a metabolic disorder thought to be due to deficiency of uroporphyrinogen I synthetase (Strand, Manning, and Marver, 1971). The result is the accumulation of porphobilinogen and aminolaevulinic acid. Periodic attacks of abdominal pain, vomiting, tachycardia, hypertension, neuropathy, and mental changes occur, sometimes after drugs, particularly barbiturates. The onset is very unusual before puberty and death may result from respiratory paralysis. Hypercholesterolaemia has been described, the β- (low density) lipoprotein fraction being increased (Lees *et al.*, 1970). Renal impairment persisting after an attack has been mentioned (Eales, Dowdle, and Sweeney, 1971), but no specific renal lesion has been described. This case presented before puberty, the hypercholesterolaemia is associated with an increase in the α- (high density) lipoproteins, and there is persistent impairment of renal function.

Case report

An 11-year-old girl was admitted to hospital with a history of 2 weeks of constant abdominal pain and vomiting, and 1 week of constipation and pain in the legs. Her father was from Guyana and her mother was Caucasian. She had never received any barbiturates, sulphonamides, or tranquillizers. On examination she was dehydrated and depressed, but her abdomen and nervous system were normal. Her pulse was 120/min and blood pressure 140/110 mmHg. Her urine turned red on standing and she had a gross excess of porphobilinogen in her urine (40 mg/24 hours), but no increase in urinary porphyrins or faecal porphyrins.

Her vomiting necessitated intravenous fluids for 24 hours. After 10 days she had completely recovered and was discharged home with a normal pulse, blood pressure, and plasma urea. She had 2 more similar attacks during the next 2 years. Neither of these was associated with any drug, nor had she started to menstruate. After recovery from her third attack, her plasma urea was found to be raised to between 58 and 65 mg/100 ml. Creatinine clearance was 25 ml/min (39 ml/min per 1·73 m^2), serum uric acid 7·6 mg/100 ml; plasma calcium, sodium, potassium, and bicarbonate were normal. Urine contained no protein, cells, or growth, and no excess of amino acids. Overnight urinary *p*H was 5·1 and osmolality 600 mOsm/l. Serum was negative for antinuclear factor. IVP showed normal kidneys. Blood pressure between attacks was normal and there had been no analgesic abuse.

Serum cholesterol was persistently raised at 340, 320, and 284 mg/100 ml. Serum triglyceride was normal at 90 and 60 mg/100 ml. Lipoprotein cholesterol ultracentrifugation showed an increase in the α- (high density) fraction at 117 mg/100 ml. The β- (low density) fraction was at the upper limit of normal at 115 mg/100 ml and pre-β- (very low density) fraction was normal at 23 mg/100 ml. She had additional abnormalities of plasma proteins. Albumin was normal at 4·2 g/100 ml, but globulin was raised at 4·2 g/100 ml, the increase being in the γ-fraction, IgG 2 g/100 ml (raised), IgM 0·315 g/100 ml (raised), IgA normal. Excess of thyroxine-binding globulin was indicated by finding serum T_3 resin uptake in the hypothyroid range, while all other thyroid function tests, serum T_4, free thyroxine index, and radio-iodine uptake were normal.

She remains asymptomatic and carries a card warning against the administration of the numerous drugs which may precipitate another attack.

Discussion

The patient had typical symptoms and signs of acute intermittent porphyria. The diagnosis was confirmed by the excess of porphobilinogen in the urine without porphyrins in the urine or faeces. She is unusual in presenting before puberty and in having no family history. Neither parent nor any of the sibs has porphobilinogen in the urine and we must assume that this patient is a new mutation.

In a large series of patients with porphyria, Eales *et al.* (1971) found a decreased creatinine clearance during acute attacks. In most patients this could be explained by dehydration and in only a very few

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