CLINICAL MANIFESTATIONS OF PRIMARY HYPEROXALURIA*

BY

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Primary hyperoxaluria is characterized during life by a continuous urinary oxalate excretion level of about 100-400 mg. (expressed as $(\text{COOH})_2 \cdot 2\text{H}_2\text{O}$) per 24 hours as opposed to the normal value of less than 45 mg. per 24 hours. Patients with this disease usually present in early childhood with multiple bilateral renal or ureteric calculi which increase rapidly in size and are composed wholly or predominantly of calcium oxalate. Nephrocalcinosis, recurrent attacks of pyelonephritis and hypertensive damage destroy the renal parenchyma and the patients usually die from renal failure later in childhood. Descriptions of cases in which the diagnosis was confirmed chemically during life and which conformed to this clinical picture have been published by Newns and Black (1953), Aponte and Fetter (1954), Archer, Dormer, Scowen and Watts (1957), Godwin, Fowler, Dempsey and Henneman (1958) and Hodgkinson (1958). The characteristic post-mortem findings are widespread destruction of the renal parenchyma by aggregates of calcium oxalate crystals, and similar deposits in the tunicae mediae of the small muscular arteries and arterioles, the myocardium, and the testis (especially the rete testis) in association with the bone trabeculae and at the growing ends of the long bones (Scowen, Stansfeld and Watts, 1959). The term oxalosis (Dunn, 1955) conveniently describes this condition of disseminated extra-renal calcium oxalate deposits.

Mulloy and Knutti (1951), Neiman, Rauber, Pierson and Gentin (1957) and Katzuni and Sandbank (1959) reported cases of infants who died apparently from renal failure at the age of a few months and in whom the findings of calcium oxalate nephrocalcinosis without stones, and of oxalosis also in Katzuni and Sandbank's (1959) case, suggest that they may have been cases of primary hyperoxaluria in which the disease followed an unusually fulminating course. Zollinger and Rosenmund (1952), Lund and Reske-Nielsen (1956) and Öigaard and Söderhjelm (1957) describe the post-mortem findings in

cases which may have been examples of primary hyperoxaluria in which stone formation began at an unusually late age. The urinary oxalate excretion was not measured in any of these cases.

The purpose of the present paper is to describe in detail the clinical features of a group of eight cases of primary hyperoxaluria arising in three families, and to comment on some aspects of the natural history of the disease. The results of an investigation of the genetic aspects of the disease, which was based on these and two other families, have been published elsewhere (Scowen, Watts and Hall, 1959) and the families have been numbered serially from four onwards in order to facilitate cross reference to that paper. Three previous families (numbers 1-3) had been investigated and the results recorded (Archer, Dormer, Scowen and Watts, 1958) before the present cases, which provided proof of some of our earlier hypotheses, became available for study.

Case Reports

Family 4. In this family there were 12 children, one dying in infancy of unknown cause. The parents are not related, and they, the unaffected children and other relatives have normal urinary oxalate excretions.

CASE 1. A boy, the second child, was admitted to hospital at the age of 10½ years because of right-sided intermittent abdominal pain, vomiting and haematuria of one day's duration. He had had a similar episode a few months previously, which had resolved without treatment. The present attack subsided spontaneously, but bilateral renal and ureteric calculi were demonstrated radiologically. He remained in hospital for two and a half months and was symptom-free except for one attack of renal colic. During this period his urine, which had initially contained leucocytes, erythrocytes and a trace of albumin, but had remained sterile on culture, became normal. The Sulkowitch test showed a low excretion of calcium, and the amino-acid pattern was normal. The blood urea was at first elevated to 49 mg./100 ml. but the serum sodium, potassium, chloride, CO_2 combining power, protein, calcium, phosphorus and alkaline phosphatase were normal.

Three months later an attack of left-sided renal colic was accompanied by the passage of a calculus, and laboratory tests gave results similar to those obtained previously. An intravenous pyelogram after this episode

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demonstrated mild bilateral hydronephrosis with slight impairment of dye excretion. Calculi were seen on both sides.

During the next 15 months he had only one mild attack of colic and then passed two small calculi which on analysis were found to consist almost entirely of calcium oxalate. The urine contained a variable slight excess of leucocytes, was usually sterile on culture and the blood urea remained below 40 mg./100 ml.

A high urinary oxalate excretion was demonstrated in March, 1958, and although he had remained in apparent good health for the previous two years, he was readmitted for further study. There were no abnormal clinical findings: marrow aspirate did not show any oxalate deposits, and the eyes were normal on slit-lamp examination. A radiograph of the kidneys showed multiple bilateral stones; there was no abnormality in the appearance of the long bones nor visible calcification in the testes. Laboratory examinations showed a sterile acid urine with excess of leucocytes, a blood urea of 45 mg./100 ml. and urea clearance of 80% with normal figures for blood sodium, potassium, chloride, CO_2 combining power, calcium, phosphate, uric acid and total protein. There was a moderate fall in serum albumin and a rise in globulin, principally gamma globulin. A series of 24-hour urine specimens showed a daily oxalate excretion in the range of 400-490 mg.

At the age of 15½ years, nine months after this admission, he had further left-sided colic, and three months later, although he had passed several calculi, it was necessary to admit him for removal of impacted calculi at the lower end of the left ureter. He had lost some weight, developed marked polyuria and anaemia, but felt fairly well. His blood pressure was 130/100: intravenous pyelography showed gross impairment of renal function and left-sided hydronephrosis, and his blood urea had risen to 100 mg./100 ml. His urine remained sterile but was loaded with leucocytes. At operation three calculi were removed from the distended left ureter. Post-operatively his blood urea rose to 292 mg./100 ml., falling gradually to its present level of 220 mg./100 ml. two months after operation. He has developed a marked anaemia and acidosis, and his daily oxalate excretion, which during the three weeks after operation ranged from 218-320 mg. with urine volumes ranging from 1,800 to 3,300 ml., has now fallen to about 100 mg.*

Calculi were analysed on several occasions and consisted entirely or mainly of calcium oxalate.

CASE 2. A girl, the third child, was investigated at the age of 13½ years because her daily urinary oxalate excretion was 202-214 mg. She had never had any urinary symptoms and was quite well. Physical examination was negative, and radiography did not show any evidence of nephrolithiasis. There were no calcium oxalate crystals in an aspirated sample of bone marrow, and no crystalline deposits could be demonstrated in the eyes by slit-lamp examination. Blood urea, urea clearance, total protein, calcium, phosphorus and uric acid values were normal;

* This patient died from renal failure three months after operation; terminally, he became oliguric and uraemic, and his urinary oxalate excretion decreased further.

the Sulkowitch reaction of the urine was Grade I, and the urinary amino-acids were normal. There was a slight increase in the serum γ , α_2 and β_1 globulins. She has been well for the last year, and oxalate excretion has remained at its initial high level.

CASE 3. A girl, the fourth child, was first admitted to hospital at the age of 7½ years with a two-day history of vomiting, colicky right-sided abdominal pain and anorexia. She had never been ill before. Radiography showed a large right kidney with numerous stones in both kidneys and ureters. The urine was acid with a slight excess of leucocytes and free of pathogenic organisms. The initial blood urea was 145 mg./100 ml. She improved during the next two weeks: further biochemical and radiological examinations did not reveal any evidence of a primary cause for her nephrolithiasis. She passed normal amounts of urine of low specific gravity, and her blood pressure remained within normal limits. Because of a further attack of colic a series of operations on the left kidney and ureter were performed for the removal of stones and she was discharged in fair condition three months after admission, her blood urea having fallen to 25 mg./100 ml. Analysis of the calculi showed the presence of calcium, phosphate and oxalate.

She was readmitted in uraemia a month later, but oliguria persisted in spite of treatment and she died 10 days later. Permission for autopsy was refused. Estimation of urinary oxalate was never performed.

CASE 4. A boy, the eleventh child, was seen at the age of 4½ years because urine examination had shown that he was excreting increased amounts of oxalate. He had not had any urinary symptoms and was perfectly well. Physical examination was negative. Radiography showed small left-sided renal and ureteric calculi. Marrow aspiration and slit-lamp examination did not show any evidence of oxalosis.

Blood urea, urea clearance, total serum protein, calcium, phosphorus and uric acid were normal. The urine gave a Grade I Sulkowitch reaction and the amino-acids were normal. Several oxalate determinations fell within the range 110-130 mg. per day.

Shortly after discharge from hospital he complained of left-sided pain, followed by the passage of a stone consisting entirely of calcium oxalate. He is now 5½ years old and has had no further symptoms, but his oxalate excretion remains high.

CASE 5. A girl, the twelfth child, was first seen at the age of 15 months because she had passed three small urinary calculi. There was no history of previous urinary disturbances. Physical examination was non-informative; the urine was acid and contained a slight excess of leucocytes; blood urea, total protein, sodium, potassium, chloride, CO_2 combining power, calcium, phosphate and alkaline phosphatase were normal. A radiograph of the abdomen showed a calculus in the right renal pelvis.

She was admitted for slit-lamp examination of the eyes and marrow aspiration, both of which were normal, and for further biochemical tests. The relevant urinary findings were a Grade I Sulkowitch reaction and an oxalate excretion in the range 90-110 mg. per day. The

blood estimations mentioned above, the urea clearance and urine amino-acids were found to be within normal limits. A further radiograph three months later showed a stone in the left renal pelvis, but she remained symptom-free for a year until she had another attack of renal pain, following which radiography showed that the calculus on the left side had disappeared. Occasional urinary oxalate estimations during the last year have shown results comparable with those quoted above.

Family 5. In this family there are two children only. The parents are not related, and they and other relatives tested do not show hyperoxaluria.

CASE 6. A girl, the first child, now aged 8 years, had painless haematuria at 2 and 3 years of age. At 5 years she had an episode of haematuria with abdominal pain and vomiting, and on radiography was seen to have bilateral renal stones and stones in the right ureter. On admission there were no abnormal physical signs and her blood pressure was normal. The urine was acid, free of cells and protein and sterile. The Sulkowitch reaction was Grade I and the amino-acids normal. Blood urea, total protein, sodium, potassium, chloride, CO_2 combining power, calcium, phosphorus and alkaline phosphatase were within normal limits. Radiographs of long bones were also normal.

Three calculi, consisting of calcium oxalate and a little phosphate, were removed from the lower end of the right ureter and she was discharged fit.

Re-investigation six months later was unhelpful, but at 6½ years she had a further attack of haematuria and the left renal stone was passed. Urine specimens tested for oxalate at this time showed increased values and she was accordingly readmitted at the age of 7 years for further investigations. There was little change in the renal opacities; bone marrow aspirate was normal and slit-lamp examination did not reveal any crystalline ocular deposits.

In addition to the tests mentioned above, the urea clearance, uric acid and serum protein electrophoresis were normal but the urine oxalate excretion averaged 170 mg. per day.

She has been followed for a period of one year and has remained well except for the passage of a stone and a mild attack of renal colic. The urinary oxalate excretion remains at its previous level.

CASE 7. A boy, the second child, now 6 years old, at 2 years developed retention of urine which was relieved by the removal of a stone from the urethra. He has since been symptom-free and was seen initially at 4 years of age, when there was no radiological evidence of nephrolithiasis.

He was admitted to hospital with his sister, and the same investigations were performed. All were normal except for the urinary oxalate excretion, which averaged 165 mg. a day.

Family 6. In this family there were four children and the parents are first cousins. The unaffected children, the parents and other relatives have normal oxalate excretions.

CASE 8. A boy, the first child, was first seen elsewhere at the age of 6 years because of nocturnal enuresis, frequency and polyuria of some duration. He had recently been rather lethargic. Physical examination and urine tests were negative, but a radiograph showed bilateral abdominal shadows thought to be calcified glands. He was then lost sight of until four years later when he was admitted to hospital with acute retention. He had had one previous such episode three years previously and the frequency and nocturnal enuresis had persisted.

He was undersized but otherwise appeared normal. His blood pressure was 120/80 and his blood urea 84 mg./100 ml. Shortly after admission he passed a stone and some gravel which were found to consist of calcium oxalate. As radiography showed bilateral renal stones he was transferred to Liverpool. Urine examination was normal but his blood pressure had risen to 130/100 and his blood urea to 110 mg./100 ml. Total serum protein and CO_2 combining power were slightly low, but serum chloride, calcium and alkaline phosphatase were normal. The phosphorus figure was a little high. A radiograph showed multiple bilateral and renal calculi with small kidney shadows, a right ureteric and two vesical calculi. The long bone structure appeared normal. He was operated upon and several calculi were removed from the small right kidney. Estimation of urinary oxalate at this stage revealed a high excretion (212 mg. per day). The urine amino-acid pattern was normal.

A month later his blood pressure had risen to 150/100 and his blood urea to 250 mg./100 ml. The vesical stones were removed at laparotomy but his subsequent course was one of slow deterioration with rising blood pressure and blood urea. Slit-lamp examination of the eyes was normal early in this terminal phase. During the fortnight before death his urine volume diminished and his urinary oxalate output fell to below 35 mg. per day. He died in uraemia 10 weeks after his transfer and autopsy was not permitted. Bone marrow aspirate taken after death contained no calcium oxalate crystals but post-mortem cerebrospinal fluid contained 0.42 mg. of oxalate per 100 ml.

Discussion

These are all classical cases of primary hyperoxaluria, except for Case 2 who has no urolithiasis although she is now almost 14 years old. The urinary oxalate excretion values are all between about 100 mg. per 24 hours and 400 mg. per 24 hours, and the individual values cannot be correlated with the severity or the apparent age of onset of the urolithiasis. The urinary oxalate excretion decreases during the last weeks of life as the terminal uraemic illness progresses, and we think that this may be associated with a phase of rapid oxalate deposition in the kidneys with the accumulation of at least the major proportion of the extra-renal deposits. The absence of detectable oxalate deposits

in the kidneys of patients with primary hyperoxaluria several years before death and in scarred pyelonephritic areas of the kidneys of one patient at autopsy (Scowen, Stansfeld and Watts, 1959; and unpublished observations), as well as the apparently normal bone development, except possibly when there has been prolonged renal failure, in spite of the calcium oxalate deposits at the growing ends of the bones at autopsy, are in conformity with this suggestion. Direct evidence of oxalosis during life was not obtained by sternal marrow aspiration biopsy or by slit-lamp examination of the eyes. It may be that trephine-biopsy of a cancellous bone or biopsy of a small muscular artery would be more informative in this respect.

Oxalosis only occurs if renal failure is accompanied by an abnormally increased endogenous oxalate production. There is no satisfactory method for the measurement of the blood oxalate level (see for example Barrett, 1943), but the observation that detectable amounts of oxalate were present in the cerebrospinal fluid and pleural effusion of the case reported by Scowen, Stansfeld and Watts (1959) and in the cerebrospinal fluid in Case 8 suggests that the concentration of this anion may be raised in the body fluids generally in the terminal stage of the disease.

Except for evidence of renal failure, the elevated urinary oxalate excretion was the only abnormal pathological finding in all of these patients. The value of this relatively simple diagnostic procedure in differentiating primary hyperoxaluria from other causes of juvenile urolithiasis, which do not carry such a grave prognosis, merits emphasis: Case 4 was diagnosed by this means before he presented with the clinical manifestations of renal calculi. Cases 1 and 8 illustrate the inexorable course of the disease and the failure of surgical intervention to influence its uniformly bad prognosis. All of our patients who were investigated in the pre-uraemic stage of the disease had normal serum uric acid levels. This is of interest in view of Aponte and Fetter's (1954) suggestion that the hyperuricaemia, which they observed in three cases with renal impairment, indicated that the disease was in some way associated with an abnormality of purine metabolism.

Although there are no reported cases of primary hyperoxaluria in patients whose urinary oxalate excretion was measured immediately after birth, there are clinical and pathological grounds for suggesting that the underlying error in the disease may be present at that time. The multiple incidence of the disease within sibships (Families 4 and 5 of this report) in the absence of any abnormality in the parents or more remote relatives, and the occurrence

of one consanguineous parentage in the total of eight families which have been studied in our laboratories (Archer *et al.*, 1958; Scowen, Watts and Hall, 1959) are compatible with the disease being due to the operation of a rare recessive character; the two sexes appear to be equally affected both in number and severity. However, Shepard, Krebs and Lee (1958) reported a family in which hyperoxaluria was present in two and possibly three successive generations, suggesting a dominant type of hereditary pattern. It may be that this apparently dominant type of inheritance resulted from the mating of a subject who was homozygous for the recessive gene with the corresponding heterozygous subject (cf. Garrod's (1908) explanation of the apparently rare dominant type of inheritance of alkaptonuria). If this were so, it is curious that the presumably homozygous parent does not show any evidence of stone formation. An alternative explanation is that there are two different metabolic lesions which cause excessive oxalate excretion and that each has its own pattern of inheritance. There is evidence that a metabolic error involving one of the pathways of glycine metabolism results in excessive endogenous oxalate production in cases of the type which we have described (Watts, Scowen and Crawhall, 1959).

Summary

The clinical features of eight cases of primary hyperoxaluria occurring in three families, in one of which the parents were first cousins, are reported and the literature dealing with similar cases is briefly reviewed.

Measurement of the urinary oxalate excretion, which is always raised, is essential to distinguish these patients from other cases of juvenile urolithiasis which do not carry such a grave prognosis.

The precise level of the urinary oxalate in individual cases cannot be correlated with the apparent age at which stone formation begins or with its rate of progression. A marked diminution in the urinary oxalate excretion characterizes the terminal uraemic phase of the disease which may or may not follow a period of chronic renal failure.

Microscopic examination of aspirated sternal bone marrow and slit-lamp examination of the eyes for evidence of oxalate deposits have not been helpful in assessing the prognosis of individual cases and have given no indication of the development of oxalosis (disseminated extra-renal oxalate deposits). It is suggested, on the basis of indirect evidence, that this occurs only late in the evolution of the disease.

There appears to be no way of preventing the formation of calculi and the management of these patients conforms to the surgical practice in other cases of recurrent urolithiasis, the cause for which cannot be removed.

Hyperuricaemia was not encountered in these cases.

The familial incidence of the disease is compatible with its being due to the operation of a rare recessive genetic character.

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