Nephronophthisis (Medullary Cystic Disease)

Renal medullary cystic disease, first described by Smith and Graham in 1945, is characterized by progressive renal insufficiency, hypotonic polyuria, negative or sparse urinary findings, and normal blood pressure. The kidneys are uniformly contracted and show cystic changes in the medulla as well as in the cortex. Renal histology shows interstitial nephritis with marked periglomerular and peritubular fibrosis and thickening of tubular basement membrane. A closely related nephropathy has been reported and termed ‘familial juvenile nephronophthisis’. Recently several authors (Strauss and Sommers, 1967; Herdman, Good, and Vernier, 1967; Mongeau and Worthen, 1967; Axelsson and Ödlund, 1968) have suggested that these two disorders might indeed be identical. An example of nephronophthisis, previously unreported in British or Indian literature, is described.

Case Report

A 4½-year-old boy was admitted for the investigation of renal rickets. He was the product of a term normal pregnancy. Excessive thirst and frequent passage of large amounts of urine were reported to have been ‘always’ present. Shaking of his eyes was noticed in early infancy. Weakness and bowing of his legs appeared at about the age of 2 years and gradually progressed. At 2½ years rickets with anaemia was diagnosed by a local doctor who prescribed vitamin D and iron. Despite therapy, his disability continued to increase till at 4 years he could not walk unaided. The finding of a raised blood urea level prompted his referral to this hospital.

A history of urinary tract infection or haematuria was denied. Examination revealed a pale, poorly developed child. His weight was 15 kg and height 97·5 cm. The blood pressure was 100/70 mm Hg. A fine horizontal nystagmus was present. The optic fundi were normal. Extremities showed severe rachitic deformities with a marked genu valgum.

Hb 7·5 g/100 ml, blood urea 120 mg/100 ml, serum creatinine 3·8 mg/100 ml, creatinine clearance 9·5 ml/min, serum calcium 8·6 mg/100 ml, serum phosphorus 5·3 mg/100 ml, alkaline phosphatase 67 KA units, blood pH 7·35, and bicarbonate 17·5 mEq/l. The serum values of proteins and cholesterol were within the normal range. ECG and audiogram were normal. Multiple urinalyses showed a maximum specific gravity of 1006. Proteinuria and glycosuria were absent and no cells or casts were seen in the sediment. Several urine cultures were sterile. The urinary amino acid chromatogram was normal. X-rays of the long bones showed advanced rachitic changes. An intravenous pyelogram faintly visualized the kidneys which were small with regular outlines. The chromosomal pattern was normal.

On a daily sodium intake of 35 mEq/l, his urinary sodium excretion averaged 42 mEq/24 hours. A 12-hour overnight water deprivation preceded by an intramuscular injection of 2·5 units of vasopressin tannate in oil resulted in a maximum urine osmolality of 158 mOsm/kg.

Renal histology. A percutaneous renal biopsy specimen, representing only cortical tissue, revealed varying degree of glomerular hyalinization. An occasional glomerulus appeared normal. Hypercellularity, crescent formation, and capillary basement membrane thickening were absent. Dilatation and atrophy of the tubules with thickening and wrinkling of the tubular basement membrane, periglomerular, peritubular, and
interstitial fibrosis with marked round cell interstitial infiltration were present (Fig.).

**Family survey.** No member had suffered from a similar disorder. Examination of the parents, who were unrelated, and three older sibs showed no abnormality. Their urinalyses were negative and in each case specific gravity of over 1020 was achieved following overnight fluid deprivation.

**Discussion**

This patient showed features common to the renal disorders known as medullary cystic disease and familial juvenile nephronophthisis. He had polyuria and polydipsia since infancy, but significant handicap was noticed only when azotaemic osteodystrophy was clinically manifest. The development of renal insufficiency in this disorder is so insidious that it is rarely detected in the preazotaemic stage. Anaemia, often disproportionate to the degree of uraemia, may be a presenting feature. Hypertension is rare except in terminal stages. Nystagmus, as present in this patient, has been observed in association with medullary cystic disease (Herdman et al., 1967). Similar familial nephropathies with associated ocular abnormalities (tapetoretinal degeneration, retinitis pigmentosa) have been claimed to represent separate entities (Schimke, 1969).

The renal dysfunction in nephronophthisis is essentially distal tubular, as manifested by hypos thenuria, sodium wasting, and impaired urinary acidification (Herdman et al., 1967). Recently, evidence of minimal proximal tubular incompetence has been obtained by Giselson et al. (1970). The earliest abnormality seems to be a failure of water reabsorption from collecting ducts. Excessive and sometimes massive natriuresis, though unimpressive in the present case, is usual in nephronophthisis. Balance studies indicate that besides mechanisms held responsible for sodium wasting in azotaemia (viz. hyperfiltration and increased osmotic load per nephron) a distal tubular and medullary defect of sodium transport may account for the natriuresis in this disorder (Better et al., 1969).

There is now little doubt that many of the patients previously reported as ‘salt-losing nephritis’ were examples of nephronophthisis (Axelson and Ödlund, 1968).

The pathological findings in this disorder are distinctive. Uniform renal shrinkage with cortical thinning, varying degrees of medullary and cortical cystic changes (not always gross), absence of intrinsic glomerular pathology, thickening of tubular basement membrane, and obvious interstitial changes are characteristic. Immunofluorescent staining has shown no abnormality. Electron microscopy has revealed thickening and a peculiar lamination of tubular basement membrane, and microdissection studies have shown cyst formation in the medullary collecting ducts and at the junction of collecting ducts with a common duct (Herdman et al., 1967).

The disorder is usually familial. Autosomal recessive as well as dominant modes of transmission have been suggested and, as in the present case, sporadic instances have also been recorded (Mongeau and Worthen, 1967). In some cases the asymptomatic heterozygote may be detected by
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tests which assess distal tubular function (Broberger Winberg, and Zetterström, 1960). The disorder may appear at different ages and have variable rates of progression, even within the same family, but it usually takes a rapid course in childhood, while a more protracted course is common in adults (Axelsson and Ödlund, 1968).

The aetiology of nephronophthisis is obscure. Bacterial infection is not considered to play a role in its pathogenesis. It has been postulated (Mongeau and Worthen, 1967) that the tubular damage might be caused by a 'toxin' resulting from an inborn metabolic error.

Summary

A sporadic example of an uncommon congenital nephropathy, previously described as medullary cystic disease or familial juvenile nephronophthisis, is reported. The patient, a 4½-year-old boy, had developed polyuria and polydipsia in early infancy followed by manifestations of azotaemic osteodystrophy. He also had a congenital nystagmus. His blood pressure was normal. Investigations revealed vasopressin-resistant hypothenuria and minimal salt wasting but otherwise normal urin analyses. The renal histology was typical of nephronophthisis.

REFERENCES


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Haemagglutination Reaction in Indian Childhood Cirrhosis Indicating Viral Aetiology

Indian childhood cirrhosis or infantile cirrhosis has a special lure for Indian investigators as it is a disease peculiar to Indian children. Its aetiology still remains an enigma. Several possibilities have been postulated, but a viral aetiology is generally favoured. Attempts to identify the hypothetical virus by histopathological (Achar and Raju, 1951) or electron microscopical means or by animal transmission experiments have been inconclusive. Morrison and Hoyt (1957) described a heteroagglutination test with greater specificity for viral hepatitis. This was further confirmed by its higher positivity in adult cirrhosis of viral aetiology, as compared to the non-viral group of cirrhosis (Morrison et al., 1961). Their results showed that the application of the haemagglutination tests in Indian childhood cirrhosis could prove to be an indirect method of investigating the relation of viruses with this type of cirrhosis in children.

Material and Method

One hundred cases of infantile cirrhosis and 25 normal controls were investigated. The disease was diagnosed primarily on the clinical features of a firm enlarged liver, splenomegaly, jaundice, and ascites, with other associated features of liver failure; where possible, liver biopsy was done (38 cases). The controls were healthy children belonging to the same age group as the cirrhosis cases; none had suffered from jaundice, or had any family history of cirrhosis; normal liver function tests were recorded in all.

Haemagglutination test. The procedure adopted is a modification of the original Hoyt and Morrison test as described by Morrison et al. (1960). The conventional scoring (+ to ++++) was used in the readings.

Observations and analysis. One hundred cases of Indian childhood cirrhosis—87 males and 13 females in the age group 7 months to 4 years—were studied. 7 cases were in the early stage of the disease, 54 presented in the intermediate stage, and 39 in the late stage. According to the clinical course of the disease, 41 cases belonged to the subacute group, 43 to the acute, and 16 were of the fulminant type.

The haemagglutination test was positive in 83 out of the 100 cases as against 2 of the 25 controls (Fig. 1). These results are highly significant. The positivity of the test was directly related to the severity of the clinical course and to the stage of the disease (Fig. 2), though there was no significant correlation between the haemagglutination titres and the clinical picture, except in the acute and fulminant cases. However, there was no
Nephronophthisis (medullary cystic disease).

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