HEREDITARY RENAL DISEASE, RETINITIS PIGMENTOSA AND OTHER ANOMALIES*

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The association of retinitis pigmentosa and hereditary renal diseases has only recently been described.[1,2] While hereditary renal diseases may comprise a wide range of disorders,[3-5] their presentation with both glomerular and tubular dysfunction has not been recognized. The frequent combination of eye, ear and renal disease with X-linked transmission[6] introduces the possibility that the above represents partial expression of a more complete syndrome. The 2 siblings to be described show evidence of familial renal, ocular, auditory and haematological abnormalities which may be compatible with a greater degree of expression of the same syndrome.

CASE REPORTS

Case 1

A 15-year-old Indian female presented with a 7-year history of episodic swelling of the legs, and of night-blindness with progressive deterioration of vision. There was no history of loin pain, haematuria, or swelling of the face. The facies showed striking bilateral ptosis (Fig. 1). There was a single transverse palmar crease. The typical picture of retinitis pigmentosa with attenuated arterioles, typical 'bone corpuscle' pigment clumping, but no optic atrophy, was seen. There was no evidence of cystinosis on slit-lamp examination. Visual acuity was 6/12 in both eyes. Apart from the ptosis, the ocular movements were normal. The rest of the general examination was normal, and the secondary sexual characteristics were well developed.

Special investigations. The haemoglobin concentration was 11·5 G/100 ml. and the MCHC 31. There were 9,000 white blood cells/cu.mm., with a normal differential count; the peripheral smear showed an elliptocytosis. The erythrocyte sedimentation rate was 33 mm. in 1 hour (Westergren) and the blood urea concentration was 18 mg./100 ml.

Further results obtained were: serum sodium 134 mEq./litre, serum potassium 4·3 mEq./litre, serum

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chloride 101 mEq./litre, serum calcium 10·0 mg./100 ml., serum phosphate 3·7 mg./100 ml., serum cholesterol 260 mg./100 ml. and Kolmer cardiolipin negative. Haemoglobin electrophoresis and chromosomal analysis were normal.

Urinalysis and tests of renal function showed pH 6·5, albumin ++, WBC ±5/high-power field, a single positive urine culture with *E. coli* > 100,000 organisms/ml., creatinine clearance 17·6 ml./min./sq.m., and a normal intravenous pyelogram. Urine concentration and dilution tests were normal and there was no glycosuria. Urinary chromatography revealed a panaminoaciduria. The urinary titratable acidity was 8·5 mEq./24 hours, and the ammonia excretion 12·3 mEq./24 hours. The short ammonium chloride test,[6] despite increasing the pre-existing systemic acidosis significantly, failed to reduce the urine pH below 6·0, thereby confirming the existence of a renal tubular acidosis.

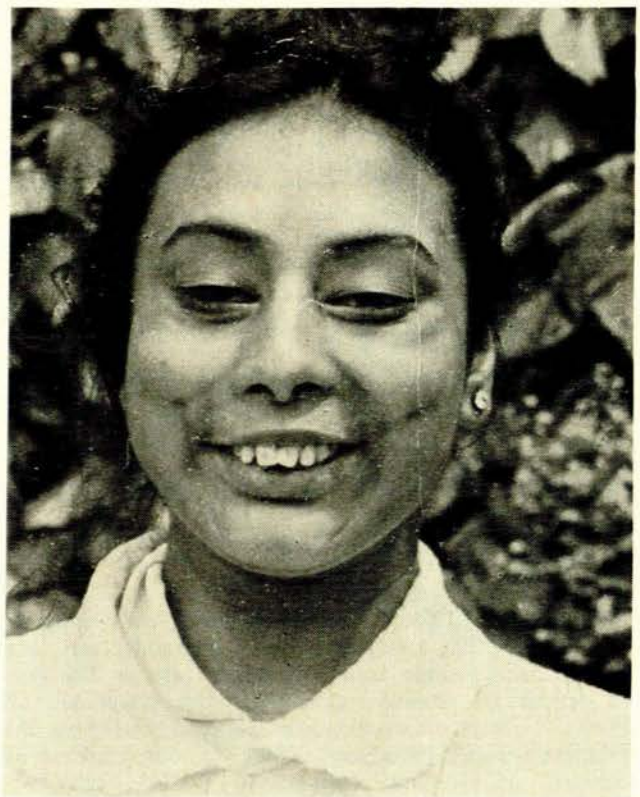

Fig. 1. Case 1, see text.

Case 2

The 23-year-old female sibling of case 1 presented with a history of ill health for many years. This included night-blindness which had been present since early childhood and which was worsening; weakness; lassitude and increasing deafness. The presence of ptosis, and resemblance to her sibling, can be seen in Fig. 2. The typical picture of retinitis pigmentosa was seen as in case 1. Visual fields showed a severe peripheral constriction with visual acuity reduced in both eyes to 6/60. Audiometry confirmed a unilateral nerve-deafness. The remainder of the examination was normal.

Special investigations. Her haemoglobin concentration was 13·5 G/100 ml., her MCHC was 35, and she had 7,000 white blood cells/cu.mm. Erythrocyte sedimentation rate was 45 mm. in 1 hour (Westergren), and the peripheral smear was normal. Other tests gave the following results: blood urea 25 mg./100 ml., serum sodium 137 mEq./litre, serum potassium 4·3 mEq./litre, serum chloride 100 mEq./litre, serum calcium 10·0 mg./100 ml.; serum phosphate 4·0 mg./100 ml., serum cholesterol 270 mg./100 ml., plasma albumin 3·5 G/100 ml., plasma globulin 2·9 G/100 ml., Kolmer cardiolipin negative. Radiographs of the spine showed increased vertical striation suggestive of multiple haemangiomata (Fig. 3). Radiographs of the skull and chest and skeletal survey were normal.

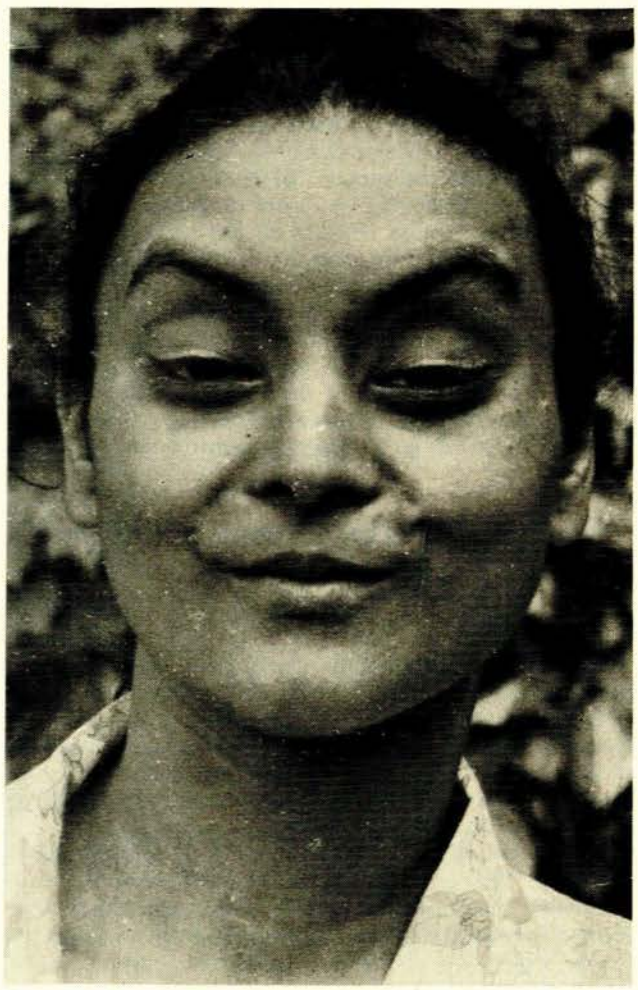

Fig. 2. Case 2, see text.

Urinalysis and tests of renal function showed: Urine pH 6·5, albumin ++, WBC ++/high-power field with a single positive culture of *E. coli* > 100,000 organisms/ml. Creatinine clearance was 18·0 ml./min./sq.m., and an intravenous pyelogram was normal. Urine electrophoresis

showed no features of tubular proteinuria. Urine concentration and dilution tests were normal, and there was no glycosuria or aminoaciduria. The urinary titratable acidity was 9·3 mEq./24 hours, and the ammonia excretion 6·2 mEq./24 hours. Ammonium chloride loading, as in case 1, produced a significant increase in the pre-existing acidosis but failed to lower the urine pH below 6·0, thereby confirming the existence of the renal tubular acidosis.

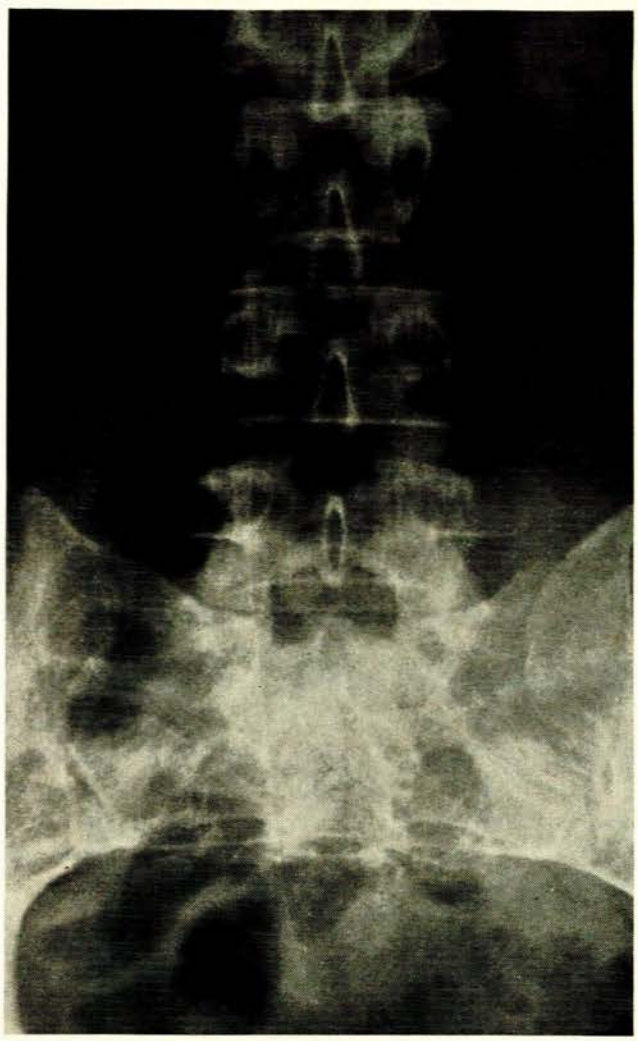

Fig. 3. Radiograph of spine shows prominent vertical striation of vertebrae.

Case 3

An Indian male of 26 years was admitted to hospital 4 years before his siblings, with malignant hypertension and uraemia from which he died 10 months later. His resemblance to his siblings (Fig. 4), glycosuria and proteinuria suggested a similar condition, but no data were available.

Investigation of the family pedigree revealed a high degree of consanguinity, in that the patients' father was married to his own niece. Of the offspring of the consanguineous marriage, 2 are affected with an ailment from which possibly a third died; 2 died in infancy of an unknown illness, and 4 are alive and apparently asymptomatic. Examination of these individuals showed no clear evidence of auditory, ophthalmic or renal disease.

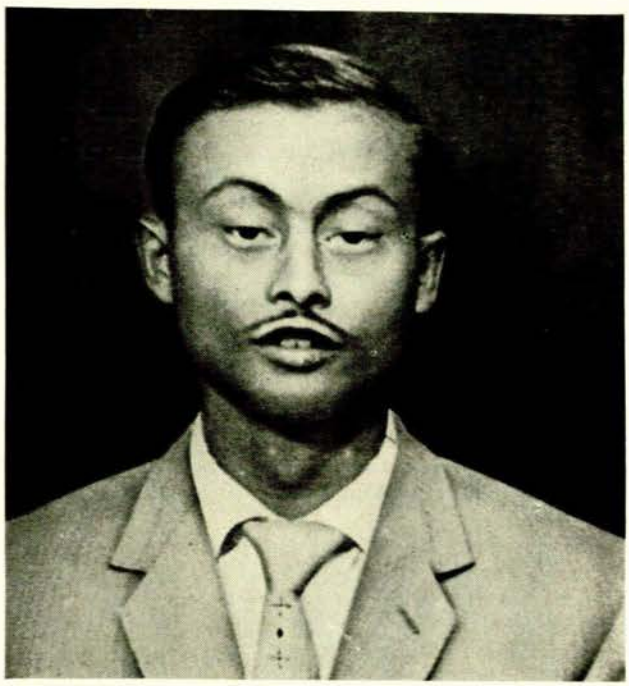

Fig. 4. Case 3, see text.

DISCUSSION

Hereditary renal diseases may present with a nephritis-type lesion, or with tubular defects.[1-5] Hereditary nephritis itself may occur either as an isolated defect, or (more frequently) with hereditary nerve-deafness, when it is referred to as Alport's syndrome. The nature of the disorder, whether a pyelonephritis or a glomerulonephritis, is not clear on clinical or pathological grounds.[7-10] The only consistent findings on urinalysis are proteinuria and the presence of red and white cells, and casts.[11]

That the patients have a nephritis-type lesion is suggested by the proteinuria, the diminished glomerular filtration rate, and the presence of casts, red and white cells and organisms in the urine. The last findings may be explained on the basis of an acquired pyelonephritis. However, the findings are quite consistent with the observation that patients with hereditary nephritis are more prone to renal infections.[8] Furthermore, the presence of a nephritis-type lesion in 3 members of a family, one of whom also has nerve-deafness, in association with a panaminoaciduria and other stigmata of hereditary disease, would suggest that the renal disease itself has a hereditary basis. The panaminoaciduria is also significant in its recognized association with hereditary but not acquired renal disease.[12,13]

Renal tubular acidosis may occur either as a primary hereditary disorder or secondary to a variety of other hereditary or acquired diseases.[14] The presence of renal tubular acidosis was suggested by the systemic acidosis

associated with diminished urinary titratable acid and ammonia excretion, and confirmed by the ammonium chloride test in which the urinary pH fell only to 6·0—well above 5·4, the lower diagnostic limit in renal tubular acidosis.[15] In the light of the evidence that the renal disease is probably hereditary, an acquired 'pyelonephritis' cannot be incriminated as the cause of the tubular acidosis, which would thus also appear to be inherited. Any postulate that the tubular acidosis itself might be the cause of an acquired 'pyelonephritis' can be discounted by the evidence that has already been discussed in favour of the nephritis being hereditary, and by the observation that tubular acidosis is unlikely to produce a pyelonephritis in the absence of nephrocalcinosis.[15]

Retinitis pigmentosa has been associated with a variety of manifestations ranging from neuropsychiatric,[16-19] metabolic[17,20] and haematological[21] to auditory[22] and renal.[1,2,23] In these patients ptosis and nerve-deafness represent neurological and auditory features, and elliptocytosis a possible haematological manifestation, particularly as acanthrocytosis of red cells and retinitis pigmentosa are well associated. Cystinosis as a cause of the Fanconi syndrome is well recognized; as an associate of retinitis pigmentosa it is less well known. No evidence of cystinosis was found.

The combination of retinitis pigmentosa and renal disease is rare. The patients described by Jackson and Linder[2] had the features of the Fanconi syndrome and retinitis pigmentosa. They also showed some glomerular dysfunction but no casts and cells in the urine, and minimal proteinuria, which might have been of the tubular variety,[24] i.e. they had no clear features of a nephritis-type lesion. While other varieties of ocular defects have been associated with Alport's syndrome for some time,[10,25] the first description of a nephritis-type lesion with retinitis pigmentosa was presented by Meier and Hess.[1] Their patients showed proteinuria and glomerular dysfunction but no tubular acidosis or aminoaciduria. This is the first paper in which the association of retinitis pigmentosa with a renal disease that has features of both a nephritis-type lesion and of tubular dysfunction has been described.

The peculiar striated appearance of the spine on radiography remains unexplained. It may represent a developmental anomaly, as may the presence of a single transverse palmar crease.

That the various conditions described above are familial seems fairly certain. In view of the known hereditary association of these disorders with one another it is reasonable to postulate a genetic transmission. The X-chromosome may be significant in this regard in view of the observation by Perkoff[3] that almost one-half the diseases of man that have been accepted as X-linked or probably X-linked are diseases of the eyes, ears and kidneys.

SUMMARY

A family is reported in which 2 siblings presented with retinitis pigmentosa and hereditary renal disease, from which possibly a third died.

Apart from the rarity of the combination of hereditary renal disease and retinitis pigmentosa, the particular pattern of renal disease with features of both a nephritis-type lesion and of renal tubular acidosis appears to be unique.

It is possible that hereditary renal disease, retinitis pigmentosa and the other associated anomalies are transmitted by closely linked genes, the variable expression of which provides a spectrum of overlapping disorders.

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