Familial juvenile nephronophthisis, Jeune's syndrome, and associated disorders

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SUMMARY Fourteen patients with familial juvenile nephronophthisis are described, eight of whom displayed one or more additional disorders. One boy with short limbed dwarfism and an abnormal chest was considered to have Jeune's syndrome; review of the published reports supports the view that nephronophthisis is the principal cause of renal failure in this disorder. Another patient with renal failure and retinitis pigmentosa at presentation developed progressive neurological and neuromuscular impairment leading to the discovery of ragged red fibre disease (mitochondrial cytopathy). Cardiomyopathy was present in this and one other patient. Tapeto-retinal degeneration, hepatic fibrosis, cerebellar ataxia, and oculomotor apraxia were among the other disorders encountered. Three patients presented in extremis with acute heart failure and irreversible oligo-anuria and this complication developed in another child who was already known to have nephronophthisis. Awareness of this disease and its associations is important for early diagnosis and appropriate management.

Familial juvenile nephronophthisis, first described in 1951,¹ is a chronic disease characterised clinically by polyuria, growth failure, and invariable progression to renal failure during childhood.² In the early stages of the disease there may be little or no morphological abnormality of the kidneys but later medullary cysts may form, while biopsy shows noticeable tubular atrophy, severe interstitial damage, and secondary glomerular obsolescence.^{2 3} The condition is inherited as an autosomal recessive and there may be a family history of consanguinity.^{2 3}

In recent years various abnormalities affecting other systems have been found in association with familial juvenile nephronophthisis. These include skeletal abnormalities,⁴⁻⁷ hepatic fibrosis,⁸⁻¹⁰ tapeto-retinal degeneration,¹¹⁻¹⁵ cerebellar ataxia,^{4 6 10 15} and mental retardation.^{1 9 12 15} The condition has also been found in association with ragged red fibre disease (mitochondrial cytopathy), a disease complex in which neuromuscular involvement is a predominant feature.¹⁶

Although renal involvement in Jeune's syndrome (asphyxiating thoracic dystrophy) is well described,¹⁷⁻²² a direct link with familial juvenile nephronophthisis is not widely recognised. Similarly, the bony abnormalities associated with the

latter disorder have not been linked with Jeune's syndrome, except on one occasion.²³

We report on 14 patients with familial juvenile nephronophthisis seen at Guy's Hospital since 1971, eight of whom had additional disorders. The series includes a child with an abnormal chest and short limbed dwarfism who presented with acute circulatory overload and in whom a retrospective diagnosis of Jeune's syndrome was made. The link between familial juvenile nephronophthisis and Jeune's syndrome is discussed, and the published reports on the renal lesion in Jeune's syndrome are reviewed. We also describe an association between familial juvenile nephronophthisis and cardiomyopathy in two patients, one of whom had mitochondrial cytopathy.

Patients

Table 1 gives the relevant clinical data on the 14 patients with familial juvenile nephronophthisis. The diagnosis was established by percutaneous or open renal biopsy in all cases. Histological requirements for diagnosis included the presence of diffuse tubulo-interstitial damage with tubular atrophy and moderate round cell infiltration together with a variable degree of glomerular sclerosis and fibrosis.

Table 1 Associated abnormalities in 14 children with familial juvenile nephronophthisis

Case no	Age	Sex	Presentation	Associated abnormalities						Outcome
				SA	HF	RP	CA	CM	Other	
1	7	M	Short limbed dwarfism, hypertension, and circulatory overload	+++	+	+	-	??	Jeune's syndrome	Successful cadaver transplant; renal artery stenosis
2	13	F	Anaemia, growth failure, retinal disease, and renal insufficiency	-	+	+++	+++	+++	Mitochondrial cytopathy (see text)	Successful cadaver transplant; died in cardiac failure 18 months after transplantation
3	13	M	Polyuria, polydipsia, and chronic renal failure	-	-	-	+	-	Oculomotor apraxia	Live-related transplant failed after 4 years (chronic rejection). Recent successful cadaver transplant
4	5	M	Anaemia, hepatosplenomegaly, acute on chronic renal failure	-	+++	-	-	-		Successful live-related transplant; splenectomy; cirrhosis, with grade 1 varices
5	5	F	Renal insufficiency and pulmonary oedema	-	-	-	-	++		Successful cadaver transplant
6	11	F	Acute renal failure with hypertension and circulatory overload	-	-	++	-	-		Continuing ambulatory peritoneal dialysis
7	22	F	Polyuria, polydipsia, and chronic renal failure	-	-	+++	-	-		Successful second cadaver transplant
8	9	F	Growth failure, polyuria, and chronic renal failure	-	-	-	-	-	Ulcerative colitis	Successful cadaver transplant; renal artery stenosis
9	5	M	Polyuria, polydipsia, and failure to thrive	-	-	-	-	-		Chronic renal failure
10	9	F	Chronic renal failure	-	-	-	-	-		Chronic renal failure
11	13	F	Chronic renal failure	-	-	-	-	-		Successful live-related transplant
12	17	M	Failure to thrive and chronic renal failure	-	-	-	-	-		Failed live-related transplant; long-term dialysis
13	13	F	Growth failure and chronic renal failure	-	-	-	-	-		Chronic renal failure
14	15	F	Enuresis and renal impairment	-	-	-	-	-		Live-related transplant; moderate chronic rejection

SA=Skeletal abnormalities; HF=Hepatic fibrosis; RP=Retinitis pigmentosa; CA=Cerebellar ataxia CM=Cardiomyopathy.

The presence of medullary cysts was not a diagnostic requirement especially as these are most unlikely to be detected on a biopsy.³ Two patients (cases 10 and 11) are siblings while case 7 had a brother with this disorder and retinitis pigmentosa who died age 10 years. The parents of case 5 are from Pakistan, and cases 10 and 11 are Turkish Cypriot; all the other patients are of British extraction. Eight of the 14 patients had one or more additional disorders and five of the more complex case histories are given in detail.

Case 1. This child was noted to have an oddly-shaped chest from birth but there was no respiratory difficulty and it was not until his second year that short stature became apparent. Detailed radiological investigation at this time showed a dyschondroplasia of indeterminate type. He then presented

aged 6 years with a six week history of progressive oedema, oliguria, and cough; nocturia had been present since he was 2 years old. He was severely hypertensive (initial blood pressure 210/180 mm Hg) with gross circulatory overload and pulmonary oedema and irreversible oligo-anuria.

Investigation showed no anaemia, urinary obstruction, or vesico-ureteric reflux; renal ultrasound showed small kidneys with poor cortico-calyceal differentiation but no medullary cysts. Percutaneous renal biopsy (Fig. 1) showed hypertrophy of arteries and arterioles consistent with hypertension; appreciable tubular atrophy, interstitial fibrosis, and lymphocytic infiltrate; and many glomeruli were either sclerotic or showing periglomerular fibrosis. The appearances were consistent with familial juvenile nephronophthisis.

Liver biopsy was performed because of persisting

Fig. 1 Renal cortex from patient in case 1 showing one glomerulus (G) obsolescent, and another with periglomerular fibrosis. There is a thickened arteriole (A), extensive loss of tubules, and a patchy lymphocytic infiltrate. (H and E $\times 250$).

hepatomegaly and showed a mild patchy portal tract fibrosis with bile duct proliferation, consistent with mild hepatic fibrosis. Fundoscopy showed pigment speckling in the periphery with no rise in activity on the electroretinogram during dark adaptation suggestive of rod degeneration, but this latter abnormality resolved after successful transplantation. The heart size remained large after the hypertension and circulatory overload had resolved and the echocardiogram showed a poorly contracting left ventricle with dyskinesis. Three months after transplantation the changes were still evident but less noticeable.

Hypertension has subsequently recurred and the aetiology of the cardiomyopathy remains uncertain. Muscle biopsy was carried out to exclude mitochondrial cytopathy, and was normal.

The patient's general appearance is shown in Fig. 2. Unusual features apart from extreme short stature ($-4SD$) include an elongated and cylindrical chest with sternal prominence, inframammary concavity, and costal flaring giving a bell shaped appearance; short limbs affecting the proximal

bones particularly; bowing of thighs, and short stubby fingers.

Radiographs taken at 15 months and 6 years of age showed similar abnormalities with more noticeable metaphysial changes latterly. In the chest there was a decrease in antero-posterior diameter with irregularity of the rib ends. Hand radiographs showed short bones and cone shaped epiphyses. There was squaring of the iliac bones with reduced acetabular angles and medial spurs (Fig. 3). The long bones showed shortening, most marked proximally. The scapulae were small and there were metaphysial irregularities of the distal humeri while the proximal femora showed metaphysial irregularity with streaky areas of sclerosis and translucency (Fig. 3). The skull and spine were normal. Both the external and radiological features were consistent with Jeune's syndrome.

Case 2. This child presented with failure to thrive at 8 months and subsequently developed non-specific anaemia. Retinitis pigmentosa was diagnosed when she was 5 years old, and by 8 years she was in chronic renal failure with severe growth failure. Renal biopsy showed severe tubular atrophy with occasional cystic dilatation, global sclerosis of some glomeruli, and increased mesangial matrix in others. The appearances were consistent with familial juvenile nephronophthisis. Eighteen months later the child received a cadaver transplant but by this time she had become ataxic with behaviour problems, recurrent convulsions associated with hypocalcaemia and unrecordable parathormone concentrations, and a grossly abnormal electroencephalogram. The graft functioned well but the child's health pursued a downward course and she developed deafness, worsening ataxia, cataracts, diabetes mellitus, ophthalmoplegia, and muscle

Fig. 2 Case 1, showing abnormal chest shape, short upper limbs especially proximally, and bowing of the thighs. Tenckhoff peritoneal dialysis catheter in situ.

Fig. 3 Case 1, pelvic radiograph showing metaphysial dysplasia of proximal femora and reduced acetabular angles.

wasting. Muscle biopsy was performed, electron microscopy of which showed the characteristic changes of ragged red fibre disease (mitochondrial cytopathy). Computed tomography of the head showed cerebral and cerebellar atrophy. Fifteen months after transplantation she developed cardiac failure, the echocardiogram showing very poor left ventricular contractility, and she died one month later. Necropsy showed atrophic kidneys with no medullary cysts, relatively well preserved glomeruli, but gross tubular atrophy; minor non-specific changes in the transplanted kidney; atrophy of the pancreatic islets; morphologically normal parathyroid glands; and the dilated heart with pale myocardium.

Case 3. This boy was noted to shake his head when fixing on an object at 4 months of age and 3 years later a diagnosis of cerebellar ataxia and Cogan's oculomotor apraxia was made. Polyuria, polydipsia, and short stature were noted at 6 years and he was found to be in chronic renal failure. Open renal biopsy showed pinpoint cortical cysts and histology was consistent with familial juvenile nephronophthisis. Two years later he required dialysis, and after undergoing host nephrectomy for hypertension he received a live donor graft. He is currently well after a second graft. His neurological symptoms are minimal and muscle biopsy has not been performed.

Case 4. This patient was found to have an iron deficiency anaemia when he was 2 years old and shortly after this hepatosplenomegaly was noted. Percutaneous cholangiogram showed a normal biliary system, while liver biopsy showed bile duct proliferation with mild portal inflammation. At this time the plasma creatinine value was 65 $\mu\text{mol/l}$. He was admitted to hospital six months later with a four day history of dyspnoea and was found to be severely hypertensive (blood pressure 240/120 mm Hg) with anaemia (haemoglobin 5.9 g/dl) and a plasma creatinine value of 500 $\mu\text{mol/l}$. Renal biopsy showed sclerosis of 50% of the glomeruli examined but little abnormality in the rest, while there was severe diffuse interstitial fibrosis with round cell infiltration. The histology was compatible with familial juvenile nephronophthisis. He received a transplant from his mother which has functioned well. Hypersplenism, severe enough to limit the use of azathioprine, became an increasing problem, however, and when he was 8 years old splenectomy was performed. At operation grade I varices and a cirrhotic liver were noted.

Case 5. This child was noted to have a poor appetite, polydipsia, polyuria, and nocturia from 18 months

of age. At 4 years short stature and severe anaemia had developed and investigations showed advanced chronic renal failure. Renal biopsy showed changes consistent with familial juvenile nephronophthisis. Four months later, she was admitted to hospital with sudden onset of severe breathlessness after a three day history of cough. There were clinical signs of severe circulatory overload with pulmonary oedema but peripheral oedema was only slight, and blood pressure was 120/70 mm Hg. A chest radiograph showed cardiomegaly and pulmonary oedema. After a short period of peritoneal dialysis and ventilation, the signs of circulatory overload regressed but oliguria persisted, the heart remained large, and the echocardiogram repeatedly showed poor myocardial contractility. Muscle biopsy showed no evidence of mitochondrial cytopathy and there was no clinical sign of retinal or hepatic disease.

She received a cadaver transplant which has functioned well, and over a two year period her heart size has returned to normal.

Discussion

The presenting features in our series of patients are consistent with those described in standard accounts of familial juvenile nephronophthisis.^{2,3} Insidious onset of renal failure, usually with a preceding history of polyuria, polydipsia, and growth failure were noted in most cases, but three children presented acutely with circulatory overload and irreversible oligo-anuria, while a fourth, who was known to have familial juvenile nephronophthisis, developed acute pulmonary oedema requiring ventilation. This sudden development in the course of the disorder is well documented both as a presenting feature and a cause of sudden death, showing the importance of early diagnosis and careful surveillance in these patients.

Of the many disorders described in association with familial juvenile nephronophthisis, those most commonly reported have been skeletal abnormalities,⁴⁻⁷ hepatic fibrosis,⁸⁻¹⁰ tapeto-retinal degeneration,¹¹⁻¹⁵ cerebellar ataxia,^{4,6,10,15} and mental retardation.^{1,9,12,15} In this series all of these abnormalities were encountered with the exception of mental retardation (although case 2 became demented as part of her neurodegenerative condition). Cerebellar ataxia was a mild feature in case 3 and occurred as part of the mitochondrial cytopathy complex in case 2. The association of ulcerative colitis in case 8 may well be coincidental.

A wide spectrum of skeletal abnormalities have been reported in patients with familial juvenile nephronophthisis. In the siblings described by

Mainzer,⁴ cone shaped epiphyses were found, together with metaphysial dysplasia of the proximal femora in the younger subject, while radiology on the patients of Bodaghi⁷ showed additional abnormalities of the iliac bones and acetabulum.

Shah²³ described three patients, all of whom died from the disorder, who displayed short limbs and thoraco-pelvic-phalangeal dystrophy characteristic of Jeune's syndrome. In one of these patients, who was described originally by Chakera⁵ and subsequently by Robins *et al*,²⁴ the diagnosis of Jeune's syndrome was made retrospectively. The concept of partial expression of the skeletal features in Jeune's syndrome is supported by Shokeir,¹⁸ who observed minor chest and hand abnormalities in three relatives of a family with affected subjects, and by Oberklaid *et al*,²² who described a 15 year old boy, two of whose siblings had some respiratory difficulty at birth, persistently small chests, and iliac abnormalities in one. The skeletal abnormalities in case 1 seem fully consistent with Jeune's syndrome, although the pelvic changes are not pronounced.

In 1955 Jeune²⁵ described two siblings who died in infancy from respiratory failure due to thoracic dystrophy. Associated features were short stubby hands with cone shaped epiphyses and trident shaped iliac bones, while subsequent development of short limbed dwarfism with metaphysial dysplasia has since been recognised. Since Jeune's original description survival beyond infancy has been well documented, the thoracic abnormality showing relative improvement, with an increased tendency towards chest infections but no late deaths from respiratory failure. The development of chronic renal failure, however, has become an increasingly recognised complication in subjects escaping death from respiratory failure in infancy.

Table 2 summarises the clinical features and renal pathology of patients from seven series of case reports on Jeune's syndrome. The cases can be broadly classified into two groups: babies dying soon after birth or in infancy owing to respiratory failure, with necropsy evidence of renal disease; and older children in whom covert renal disease was found or in whom chronic renal failure occurred. In the first group varying degrees of tubular dilatation sometimes resulting in cortical cysts were frequently found, while Bernstein¹⁹ describes an infant with cystic dysplasia and another with diffuse cystic disease. In the second group all patients showed tubular atrophy, interstitial fibrosis and infiltration, and glomerular sclerosis. Four of the authors mention the similarity to nephronophthisis, although Gruskin²⁰ found the degree of glomerular disease to be in apparent excess of the tubular damage. Hepatic fibrosis, usually mild, was frequently noted,

while four of Gruskin's patients and Edelson's²¹ case showed retinal pigmentation.

Although the renal lesion in Jeune's syndrome seems to be heterogeneous, with various forms of dysplasia predominating in infancy and early childhood, we believe the progressive lesion found in older subjects to be indistinguishable from that of familial juvenile nephronophthisis. This concept is based not only on consideration of the renal histology which is basically that of a diffuse tubulo-interstitial nephropathy with no pathognomonic feature, but also on other features common to both disease complexes such as hepatic fibrosis, retinal pigmentation, and autosomal recessive inheritance. This intriguing overlap is not necessarily restricted to familial juvenile nephronophthisis and the Jeune syndrome. Tapeto-retinal degeneration, polydactyly (a recognised feature in Jeune's syndrome), autosomal recessive inheritance, and a renal lesion which may closely resemble familial juvenile nephronophthisis or medullary cystic disease are all found in the Laurence-Moon-Bardet-Biedl syndrome.²⁶ Further systematic study of patients with these poorly understood disorders is required to clarify the links between them.

We also suggest that the skeletal abnormalities described in familial juvenile nephronophthisis might be considered as variable expressions of the Jeune syndrome and that subjects presenting with this type of short limbed dwarfism be kept under close renal surveillance. The disorder seems a common complication in patients with Jeune's syndrome who survive infancy, although there is one report of an adult with Jeune's syndrome,²⁷ while the 15 year old patient in Oberklaid's series was well with no evidence of renal disease.²² By contrast skeletal abnormalities in children presenting with familial juvenile nephronophthisis seem to constitute one of the less common disease associations.

The spectrum of severity in hepatic fibrosis accompanying this disorder is evident in our series; case 1 displaying only slight hepatomegaly with mild portal fibrosis on biopsy whereas case 3 has severe hepatic fibrosis with portal hypertension. Although case 3 required dialysis before his third birthday, his hepatic histology is dissimilar to that seen in a series of patients recently described (R Habib personal communication) all of whom had renal enlargement, histology compatible with familial juvenile nephronophthisis, and end stage renal failure before 2 years of age.

The tapeto-retinal degeneration described first by Senior¹¹ and then Loken¹² in association with familial juvenile nephronophthisis encompasses optic atrophy with blindness dating from infancy¹⁴ and pigimentary retinopathy with variable progression and

Table 2 Clinical features and renal histology in patients with Jeune's syndrome

Authors	Case	Age	Clinical features	Renal lesion	Hepatic fibrosis	Retinal pigmentation
Shokir <i>et al</i> (1971) ¹⁸	IV 17	†33 hours	Respiratory failure; enlarged kidneys	Cortical cysts arising from convoluted tubules. Some areas of glomerular sclerosis and atrophy. Bilateral vesico-ureteric junction obstruction. Scattered cortical microcysts.	+	NS
Bernstein <i>et al</i> (1968) ¹⁷	1	†7 weeks	NS	Diffuse cystic disease with irregular dilatation of cortical tubules and focal sclerosis of glomeruli.	Enlarged portal areas with tortuous dilated ducts	
(1974) ¹⁹	2	†12 days	NS			
	3	†1 month	NS	Cystic dysplasia		
	4	See Gruskin <i>et al</i> case WL				
Herdman & Langer (1968) ¹⁷	2	†4 years	Urine concentrating defect aged 2 years, followed by chronic renal failure.	Interstitial fibrosis, tubular atrophy, round cell infiltration with some tubules showing cystic change.	NS	NS
Gruskin <i>et al</i> (1971) ²⁰	MI	17 years	Died of congestive cardiac failure. End stage renal failure.	Diffuse severe interstitial fibrosis with round cell infiltration and severe tubular atrophy.		+
	GI	11 years	Urine concentrating defect.	No biopsy	NS	+
	JI	13 years	Proximal renal tubular acidosis.	Tubular atrophy and dilatation; focal glomerular fibrosis.		+
	HL	1½ years	Proximal renal tubular acidosis.	Mesangial thickening, slight tubular dilatation.		+
	WL	†4 years	Urine concentrating defect followed by chronic renal failure.	Mesangial thickening, glomerular sclerosis and tubular atrophy.		NE
Edelson (1974) ²¹	W 1	†22 days	NS	Mild generalised tubular dilatation.	+	NE
		†14 months	Urine concentrating defect, proteinuria, partial Fanconi syndrome. Died of cardiac failure.	Dilated tubules, glomerular scarring and sclerosis		+
Shah (1980) ²³	1	†6 years	Congestive cardiac failure and chronic renal failure with hypertension in case 1. All died on peritoneal dialysis while awaiting transplantation.	Pericapsular thickening, diffuse interstitial fibrosis, round cell infiltration, and disorganisation of glomeruli.	+	NS
		†4 years			+	NS
		†3 years			+	NS
Oberklaid <i>et al</i> (1977) ²²	1	†16 months	Died of respiratory failure	Glomerular and tubular cysts, increased amount of loose connective tissue and abnormal tubules surrounded by concentrically arranged collagen fibres.	+	
	4	†10 weeks		Scarring and distortion of renal parenchyma; less damaged area showed abnormal dilated tubules, small tubules; some glomeruli shrunken; thick walled vessels.		
	5	†5 weeks				
	10	†12 hours	Anaemia, hypertension, uraemia			
	2	†3 years				
	3	†5 years				
	6	†3 years	Respiratory difficulty; uraemia at 13 months. Died in renal and respiratory failure.	Cystic dysplasia and fibrous changes.	Neonatal hepatitis	

NS=not stated; NE=not examined; †=died.

handicap. In this series case 7 has tunnel vision but reasonable acuity, case 6 has severe myopia but no visual defect, and case 1 has asymptomatic pigment speckling of the retinae. Case 2 was found to have pigmentary retinopathy in the early stages of her illness but subsequently developed other features which led to the diagnosis of mitochondrial cytopathy.

The association between familial juvenile nephronophthisis and mitochondrial cytopathy—a disease complex featuring ophthalmoplegia, ptosis, pigmentary retinopathy, cerebellar ataxia, deafness, weakness, and neurodegeneration was briefly mentioned in the series of Egger *et al.*¹⁶ In fact the child mentioned in an addendum to Egger's paper is case 2 in our series. The authors also described three other children with progressive renal disease, one of whom died age 3 years in renal failure. Renal biopsy from this patient showed severe diffuse segmental glomerulosclerosis and tubular atrophy. The other patients were not biopsied but both had renal failure and in one the presenting features included polydipsia, polyuria, constipation, and a Fanconi syndrome. The outcome in patients with mitochondrial cytopathy is poor and we would advise muscle biopsy in patients with familial juvenile nephronophthisis and neuromuscular symptoms.

Cardiomyopathy was found in case 2 in the context of mitochondrial cytopathy but occurred as an isolated feature in case 5, whose muscle biopsy was normal. Cardiomyopathy has not been reported previously in association with this disorder but, as mentioned above, the sudden development of acute congestive heart failure in familial juvenile nephronophthisis is well recognised. While the circulatory overload in such cases may be purely secondary to oliguric renal failure, an unrecognised cardiomyopathy could be a contributory factor in some instances.

The coexistence of familial juvenile nephronophthisis and the various skeletal, hepatic, retinal, and neuromuscular disorders described in this paper is probably more common than is generally appreciated. A wider awareness of the association would promote earlier investigation and diagnosis of children at high risk, avoiding the late and potentially catastrophic presentation seen in several of the children in this series.

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