

Mitochondrial cytopathy presenting with focal segmental glomerulosclerosis, hypoparathyroidism, sensorineural deafness, and progressive neurological disease

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Abstract

A 6 year old boy who presented with steroid unresponsive nephrotic syndrome is reported. He was found to have focal segmental glomerulosclerosis and associated hypoparathyroidism and sensorineural deafness. The child progressed to end stage renal failure and was successfully managed by dialysis and cadaveric renal transplantation. He later developed progressive neurological deterioration and mitochondrial myopathy and neuropathy was diagnosed.

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Keywords: mitochondrial myopathy; neuropathy; focal and segmental glomerulosclerosis; renal transplantation

The coexistence of hypoparathyroidism and sensorineural deafness is well recognised. An associated renal anomaly has been reported in some individuals but a review of the literature indicates there is no consistent renal lesion. We report the clinical course of a boy with hypoparathyroidism and sensorineural deafness who was found to have focal and segmental glomerulosclerosis and who was successfully treated by cadaveric renal transplantation. This is the first reported case of long term survival in a child with this constellation of symptoms. Four years after transplant he presented with weakness of limbs and mitochondrial myopathy and neuropathy was diagnosed.

Case report

A 6 year old white boy was admitted to his local hospital with a two week history of cough, coryzal symptoms, and oedema. On admission he was normotensive and was noted to have generalised oedema, marked proteinuria, hypoalbuminaemia, and hypercholesterolaemia. A diagnosis of nephrotic syndrome was made. Investigations revealed a glomerular filtration rate of 75 ml/min/1.73 m² calculated from height and plasma creatinine, C₃ 0.90 g/l (normal range 0.75–1.75 g/l), C₄ 0.15 g/l (0.14–0.54 g/l), negative antinuclear antibodies and double stranded DNA antibodies, and no evidence of previous hepatitis B or C infection. His nephrotic state did not remit despite oral steroid therapy 2 mg/kg/day for five weeks. He was transferred to this hospital where he was found to be grossly oedematous with ascites and scrotal oedema and he was hypertensive and oliguric. He was started on daily albumin infusions with frusemide because of persisting oliguria and to reduce the severity of the oedema. He remained nephrotic despite daily infusions of methylprednisolone at a dose of 10 mg/kg/day. A percutaneous renal biopsy was undertaken and revealed typical features of advanced focal, segmental, and global glomerular sclerosis (fig 1). A diagnosis of hypoparathyroidism was made after investigation of persistent hypocalcaemia and hyperphosphataemia.

Following the histological findings he was maintained on prednisolone 2 mg/kg/day and cyclophosphamide 2.5 mg/kg/day for eight weeks; on completion he was treated with cyclosporin A 5 mg/kg/day. He rapidly progressed to end stage renal failure and was established on continuous cycle overnight peritoneal dialysis. Twenty months after presentation he received a successful cadaveric renal transplant with excellent renal function four years later (latest plasma creatinine concentration 36 µmol/l; table 1).

This boy was born to first cousin white parents at 37 weeks' gestation and delivered by elective caesarean section after an uneventful pregnancy. He had a profoundly deaf older sister who required a cochlear implant and after investigation at birth he was also diagnosed to have a severe sensorineural deafness. There was no other family history of learning difficulties, deafness, renal disease, nor hypoparathyroidism.

At 2 years of age he was admitted to hospital with an encephalitic illness which left him with

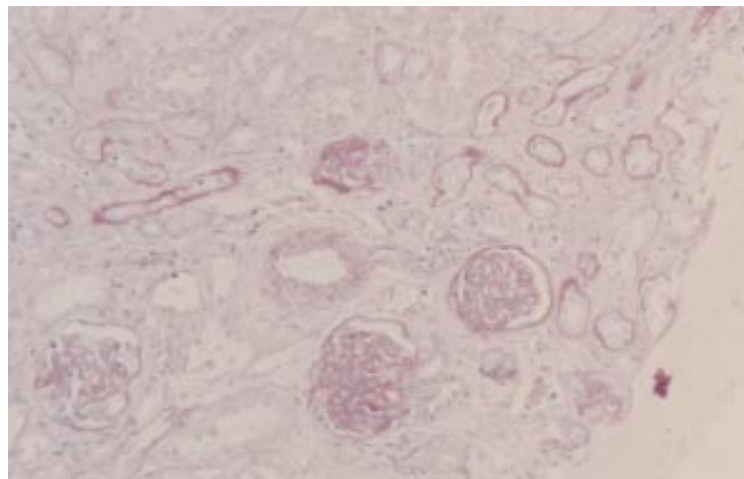


Figure 1 Renal biopsy specimen demonstrating focal glomerulosclerosis and tubular atrophy (periodic acid Schiff $\times 100$).

Table 1 Measures of renal function and nephrosis in relation to different interventions

| Intervention | Serum urea (mmol/l) | Serum creatinine (μ mol/l) | Urinary Pr/Cr ratio | Serum albumin (g/l) | GFR ml/min/1.73 m ² |
|----------------------|---------------------|---------------------------------|---------------------|---------------------|--------------------------------|
| Presentation | 5.0 | 45 | 12 000 | 25 | |
| Oral steroids | 14.6 | 60 | 14 020 | 27 | 75 |
| Intravenous steroids | 19.0 | 55 | 18 379 | 19 | |
| Cyclophosphamide | 6.5 | 50 | 7 800 | 22 | |
| Cyclosporin | 11.7 | 102 | 2 453 | 28 | |
| Peritoneal dialysis | 15.3 | 428 | 540 | 30 | 8 |
| Renal transplant | 17.4 | 61 | 54 | 33 | |
| Post-transplant | | | | | |
| 5 weeks | 14.6 | 51 | 46 | 34 | |
| 1 year | 4.7 | 32 | 18 | 33 | |
| 4 years | 8.7 | 39 | 20 | 35 | |

GFR = glomerular filtration rate; Pr/Cr = protein/creatinine ratio.

a residual mild right hemiparesis. He had stable moderate learning difficulties. At age 10 years, four years after his successful renal transplant he presented with a six month history of progressive loss of gross and fine motor functions of both upper and lower limbs. On examination he was found to have proximal weakness in the lower limbs and weakness and wasting distally in both upper and lower limbs with absent reflexes.

He had creatine kinase fluctuating between 200 and 1100 U/l (normal <200 U/l) and a raised serum lactate of 3.9 nmol/l (normal fasting 0.6–2.4 nmol/l). Magnetic resonance imaging scan showed very mild cerebral and cerebellar atrophy with abnormal high signal on T2 weighted imaging in the deep white matter. The findings were suggestive of previous encephalopathy or leukodystrophy. Nerve conduction studies confirmed the presence of a neuropathy and muscle biopsy showed ragged red fibres (fig 2), with fibres unstained in the cytochrome oxidase reaction and abnormal mitochondrial inclusions on the electron microscopy indicating a mitochondrial myopathy. No mitochondrial abnormality was detected in the renal tissue. Assay of muscle respiratory chain enzymes revealed a moderate reduction in complex III and complex I activity, however, flux assays measuring complex III and other complexes were not decreased. Mitochondrial DNA analysis of muscle excluded the MELAS

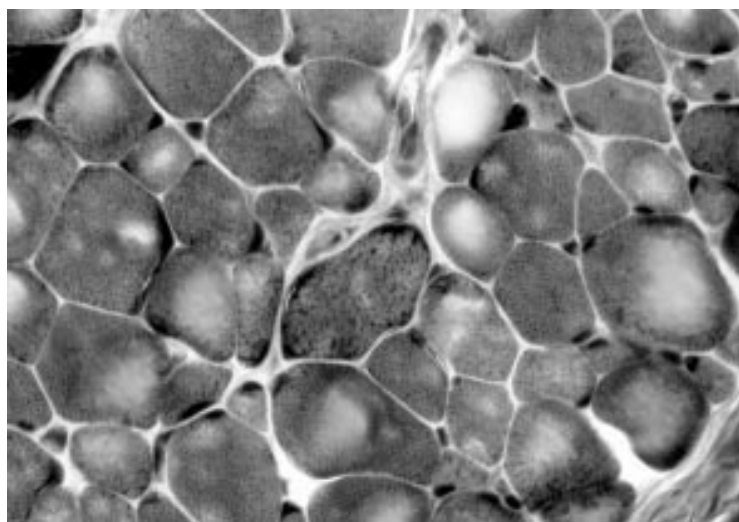


Figure 2 Muscle biopsy specimen demonstrating ragged red cell fibres (Gomori's stain \times 400).

3243 and MERF 8344 and NARF 8993 mutations. Southern blotting revealed no evidence of rearrangements; however, amplification of the genome by the long chain polymerase chain reaction revealed evidence of a rearranged molecule. The abnormality was detected using two different primer sets inferring it was unlikely that it was due to a technical artefact.

Discussion

The triad of steroid resistant nephrotic syndrome, hypoparathyroidism, and sensorineural deafness was first described by Barakat *et al.*¹ They reported two brothers both of whom died from renal failure. The first child had sensorineural deafness, developed a steroid resistant nephrotic syndrome, and was found to be hypocalcaemic and hyperphosphataemic. He had a progressive deterioration of renal function and died at 8 years of age. His sibling presented aged 3 years with the same clinical features and also deteriorated rapidly and died within two years. At postmortem examination renal histology showed a panglomerulosclerosis (consistent with end stage renal failure), absent parathyroid glands in one child and a hypoplastic gland in the other. In addition Barakat *et al* also reported male twins with similar clinical features, namely hypocalcaemia, deafness, and nephrotic syndrome who died from renal failure aged 3 years. At necropsy the parathyroid glands were fibrotic. He studied five generations of this family and although no other family members had renal disease, there were four individuals on the maternal side who had sensorineural deafness.

Several authors who described cases with a similar constellation of symptoms have subsequently cited this paper. Shaw *et al* reported hypoparathyroidism and a renal tubular defect in four cousins, two of whom also had sensorineural deafness.² Bilous *et al* described a family with an autosomal dominant mode of inheritance.³ Four of the eight affected individuals were considered fully affected because they had deafness, hypoparathyroidism, and renal dysplasia. Two others had renal dysplasia with normal hearing and were normocalcaemic and the remaining two may have had hypoparathyroidism on the basis of low calcium and sudden death in infancy. Renal dysplasia was confirmed by tissue biopsy in one and by intravenous pyelography, ultrasound, and dimer-captosuccinic acid scan in the others. Hasegawa *et al* recently reported a 2 year old Japanese girl with hypoparathyroidism, deafness, and renal dysplasia and proposed the acronym HDR syndrome (Hypoparathyroidism, Deafness, and Renal dysplasia).⁴ Their patient also had a deletion of 10p13 prompting them to speculate the gene for HDR syndrome may be situated in the deleted segment. They identified 14 reports of patients with this same deletion and noted five of these had hypoparathyroidism or hypocalcaemia (four had been diagnosed as partial DiGeorge syndrome), six had urinary tract abnormalities, and two had deafness but none had all components of HDR. We have found that neither the index

case nor his sister has any detectable abnormality of chromosome 10.

Although hypoparathyroidism and deafness are consistent features, the reported renal abnormality is variable (see table 2) with steroid resistant nephrotic syndrome and glomerulosclerosis only being reported by Barakat *et al*¹; in this respect our case is very similar to his. In our patient the histological finding was of focal and segmental glomerulosclerosis (FSGS). Although the cases reported by Barakat *et al* were noted to have panglomerulosclerosis rather than FSGS,¹ we suspect this was because the diagnosis was made on specimens obtained after death from renal failure. In contrast our patient underwent biopsy at an earlier stage of the illness, allowing a histological diagnosis to be made. The mode of inheritance has been variable, the cases reported by Barakat *et al*,¹ Shaw *et al*,² and ourselves suggesting an autosomal recessive mode of inheritance while Bilous *et al* favoured an autosomal dominant mode of inheritance.³ The finding of a deleted chromosomal segment by Hasegawa *et al* supports an autosomal dominant mode of inheritance for HDR.⁴

These clinical observations suggest that while hypoparathyroidism and sensorineural deafness may be associated, any coexisting renal abnormality is variably expressed and can include dysplasia, FSGS, or tubular abnormalities. Although Hasegawa *et al* have reported a deletion at 10p13,⁴ this was not found in our patient, suggesting the renal manifestations indicate genetic differences. It is interesting that the parathyroid gene is located at 11p11 and the nephroblastoma gene at 11p13 and, although no auditory gene has yet been located on the same chromosome, it may be that detailed chromosome studies should be undertaken of this region.

We describe a child with steroid resistant nephrotic syndrome associated with sensorineural deafness and hypoparathyroidism with similarities to four previously reported children¹ but who subsequently developed a mitochondrial disorder. We believe that there are clinical and histological reasons for considering these cases separate from HDR syndrome. It is not surprising the renal lesion did not prove to be responsive to therapies used to treat primary FSGS but dialysis and renal transplantation were undertaken successfully. We have not observed evidence of recurrence of the original disease in the transplanted organ but are unable to comment on the advisability of living related transplantation.

Learning points

- There is a rare but well recognised association between steroid resistant nephrotic syndrome, sensorineural deafness, and hypoparathyroidism.
- End stage renal failure in this case was successfully treated with a renal transplant.
- Four years after transplant our patient developed neurological deterioration. Raised plasma lactate concentrations and a muscle biopsy confirmed the deterioration due to mitochondrial cytopathy.
- We speculate that all the clinical features in our patient can be attributed to mitochondrial dysfunction.

Our patient subsequently demonstrated deterioration in motor function and was noted to have a raised plasma lactate concentration. A muscle biopsy confirmed ragged red fibres indicative of a mitochondrial myopathy. Mitochondrial cytopathies are pleomorphic diseases due to defective mitochondrial oxidative function. The system involved and severity of dysfunction determines the mode of presentation. Furthermore the clinical course is often unpredictable because the rate of deterioration in function may be variable and previously unaffected systems may become involved. Brain, muscle, heart, and pancreas are most commonly affected but other organs including liver, kidneys, and endocrine glands have also been reported to demonstrate mitochondrial dysfunction. Hearing loss ranging from mild to profound is another important feature in mitochondrial disorders. Oshima *et al* reported three cases of sensorineural hearing loss due to mitochondrial DNA mutation in MELAS,⁵ while Rosenthal *et al* reported successful cochlear implantation in a patient with MELAS, cortical blindness, and profound sensorineural loss.⁶ The renal involvement usually manifest as tubular defects but FSGS has also been occasionally described. Kurogouchi *et al* described a 27 year old Japanese woman with short stature, hearing loss, cardiac failure, and focal segmental glomerulosclerosis who was found to have the MELAS mutation.⁷ Unfortunately, despite extensive investigations we have been unable to place this child in one of the recognised syndromes associated with mitochondrial dysfunction. Mitochondrial disorders, however, are known to cause multisystem abnormalities in varying severity. We speculate

Table 2 Clinical features of cases reported in the literature compared with this case report

| | Hypoparathyroidism | Sensorineural deafness | Renal anomaly | Inheritance |
|--------------------------------------|--------------------|------------------------|--------------------------------------|-------------|
| Barakat <i>et al</i> ¹ | Yes | Yes | Steroid resistant nephrotic syndrome | AR |
| Shaw <i>et al</i> ² | Yes | Yes | Renal tubular defect | AR |
| Bilous <i>et al</i> ³ | Yes | Yes | Renal dysplasia | AD |
| Hasegawa <i>et al</i> ⁴ | Yes | Yes | Renal dysplasia | AD |
| Kurogouchi <i>et al</i> ⁷ | No | Yes | FSGS | Sporadic |
| Our case | Yes | Yes | FSGS | AR |

AD = autosomal dominant; AR = autosomal recessive; FSGS = focal segmental glomerulosclerosis.

all the clinical features in our patient can be attributed to mitochondrial dysfunction.

- 1 Barakat AY, D'Albora JB, Martin MM, et al. Familial nephrosis, nerve deafness, and hypoparathyroidism. *J Pediatr* 1977;**91**:61–4.
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- 7 Kurogouchi F, Oguchi T, Mawatari E, et al. A case of mitochondrial cytopathy with a typical point mutation MELAS, presenting with severe focal glomerulosclerosis as main clinical manifestations. *Am J Nephrol* 1998;**18**:551–6.

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