

A maternally transmitted lethal neonatal progeroid syndrome with prominent genitourinary and gastrointestinal features

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Abstract

Twin brothers and their maternal uncle with a previously undescribed neonatal progeroid syndrome are presented. In addition to progeroid features, they had pseudo-obstruction of the urinary and gastrointestinal tracts, severe leucocytosis, liver dysfunction, and low complex III and IV in muscle but not in liver. Previously described neonatal progeroid syndromes and syndromes featuring pseudo-obstruction are discussed. The two most likely aetiological mechanisms are an X linked single gene disorder or a mitochondrial disorder. The evidence for these possibilities is presented.

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Keywords: progeroid; pseudo-obstruction; mitochondria

Twin brothers and their maternal uncle presented with progeroid features and gastrointestinal and urinary tract pseudo-obstruction and died in infancy. No specific diagnosis could be made pathologically or by comparison with previously described syndromes.

Case reports

PATIENT 1

Patient 1 (III.4, fig 1) was born at term to non-consanguineous parents. Weight was 2115 g (<3rd centile), length 43 cm (<3rd centile), and occipitofrontal head circumference

(OFC) 30 cm (<3rd centile). He was noted to have several dysmorphic features including hirsutism with a low anterior hair line, a small jaw and mouth, flat philtrum, small upturned nose, folded down ears, undescended testes, micropenis, and dorsiflexed halluces. The abdomen was distended and renal ultrasound showed grossly dilated kidneys and ureters. A small patent ductus arteriosus was present. Cranial ultrasound and ophthalmological examination were normal. He had an unexpected cardiorespiratory arrest on day 4 and died. No clinical photographs were taken of this baby. The karyotype was 46,XY.

Necropsy showed a markedly hypertrophied bladder with enlarged kidneys and dilated renal pelvis and ureters, but no obstructing lesion in the urethra. The large bowel had focal areas of necrotising enterocolitis. The liver showed marked intracanalicular cholestasis but no obvious obstructive lesion in the biliary tree was identified.

PATIENTS 2 AND 3

Patients 2 and 3 (IV.1 and IV.2, respectively, in fig 1, figs 2 and 3) were monozygotic, monoamniotic twin boys, born to the sister of patient 1. Patient 1's sister and her husband are non-consanguineous and are of different cultural backgrounds. An ultrasound at 36 weeks' gestation showed hydronephrosis in both twins with one having hydroureter bilaterally as well. The bladder was reported as normal. Liquor volume was normal. At birth at 37 weeks' gestation, both infants were noted to be growth retarded, dysmorphic, and had early onset respiratory distress requiring ventilation with 100% oxygen.

Patient 2 had a birth weight of 2300 g (<10th centile), length of 42.5 cm (<10th centile), and OFC of 34.5 cm (50th centile). Multiple dysmorphic features were present and included prominent parietal bones, hair extending onto the forehead and cheeks, a very small anteverted nose, flat philtrum, micrognathia, microstomia, and a markedly distended abdomen. The anterior fontanelle was widely open. Formal ophthalmological examination did not show any definite pathology and in particular there were no cataracts.

On day 1 he had a cardiovascular collapse associated with a marked metabolic acidosis (pH 6.77, pCO₂ 67 mm Hg, HCO₃ 9.3 mmol/l, base deficit >22 mmol/l). He responded to supportive measures of intravenous albumin,

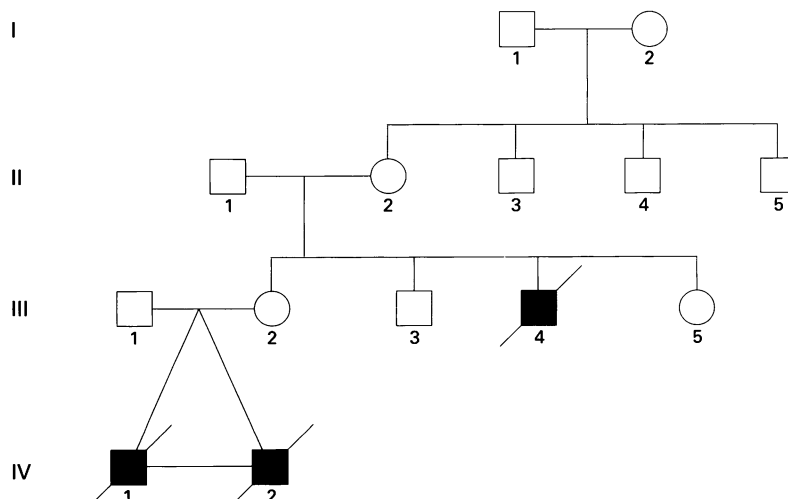


Figure 1 Family pedigree.

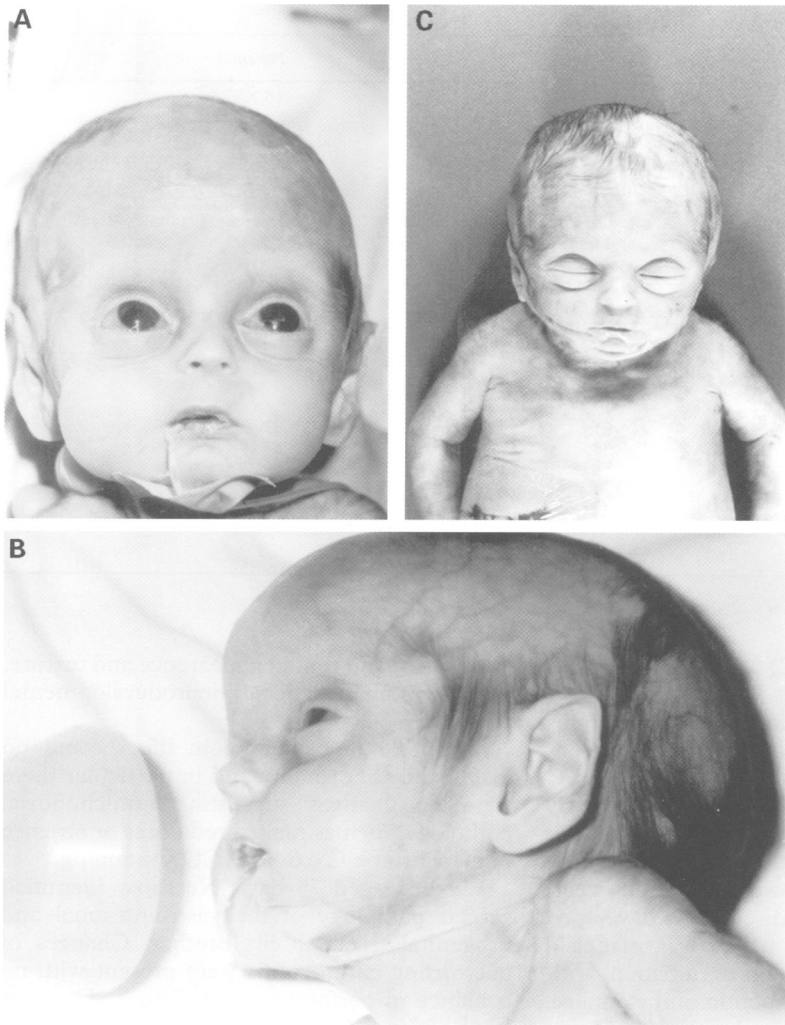


Figure 2 Facial features of patients 2 and 3. (A) Patient 3 at 56 days of age. Note the progeroid appearance with deep eyes, maxillary hypoplasia, hypoplastic nose, small mouth, and relatively large ears. The baby in fact had hair extending onto his forehead, but much of this was shaved off to facilitate intravenous access. (B) Lateral view of patient 3 at 56 days of age. Note deep set eyes and hypoplastic nose. (C) Patient 2 post mortem. Note similar features to his brother but progeroid features less well developed. (Photographs reproduced with permission.)

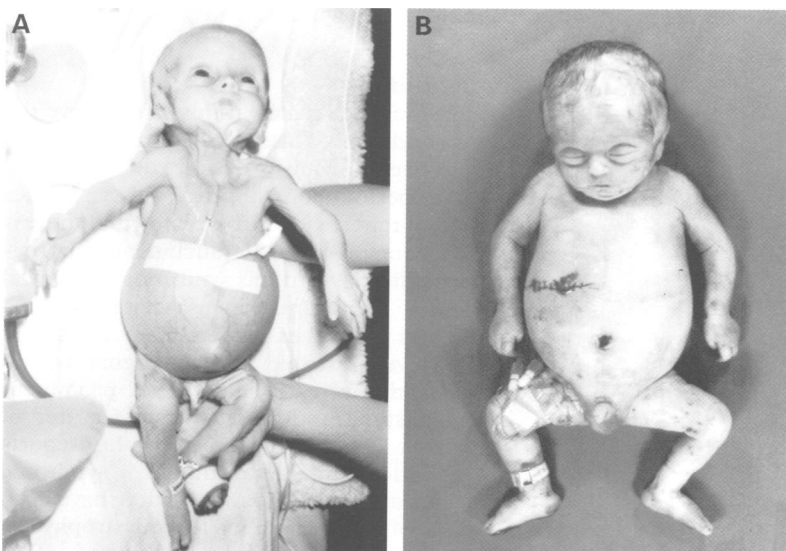


Figure 3 Whole body views of patients 2 and 3. (A) Patient 3 at 56 days of age. Note the grossly distended abdomen with lack of subcutaneous fat with buccal sparing and prominent subcutaneous veins. (B) Patient 2 post mortem. Note similar features to twin but not as well progressed given his earlier age at death.

bicarbonate, and a dopamine infusion. Liver function was abnormal with raised transaminases. Urine organic acids showed a high lactate with a milder increase of 4-hydroxyphenyllactic acid and 4-hydroxypyruvic acid. Serum ammonia was initially 364 $\mu\text{mol/l}$ ($N < 50$), but returned to normal as liver function improved without specific therapy. Plasma amino acids, very long chain fatty acids, and carnitine were all normal. The abdomen remained grossly distended throughout and he never passed meconium. Abdominal x ray at this time was notable for a gasless bowel except for a single dilated loop interpreted as being consistent with necrotising enterocolitis. Abdominal ultrasound on day 2 of life showed bilateral dilatation of the renal pelvices and ureter and a thickened bladder wall. Micturating cystourethrogram did not show any obstructive lesion. He was clinically unfit for rectal suction biopsy or barium studies of the lower gastrointestinal tract. Echocardiography showed a patent ductus arteriosus. Karyotyping was normal (46,XY). He developed hyperkalaemia secondary to acute renal failure and died on day 12.

Gross findings at necropsy were distended large bowel and dilated pelvicalyceal systems with marked dilatation of both ureters. The bladder was massively hypertrophied but no distal obstructive lesion was found. Histologically, the lungs showed resolving hyaline membrane disease and bronchopneumonia. The liver showed features of erythrophagocytosis and cholestasis without evidence of hepatitis. There was marked medial hypertrophy of the bladder wall with an increase in fibrous tissue both in the lamina propria and between muscle bundles. The bowel wall was diffusely thinned with an attenuated muscularis. Myenteric ganglion cells were present throughout and of normal appearance. Histological changes consistent with necrotising enterocolitis were found but there was no evidence of perforation or stricture. The brain showed a normal gyral pattern. There was marked softening of the posterior frontal lobes bilaterally with moderate bile staining and ischaemic/anoxic changes were confirmed histologically. Electron microscopy of liver and skeletal muscle was unremarkable and, in particular, the mitochondria looked normal.

Respiratory chain enzymology was performed on muscle and liver obtained within one hour of death using the techniques described in Rahman *et al.*¹ Citrate synthase (CS) is used as a marker enzyme of mitochondrial function and results are expressed both as a percentage of control tissue enzyme activity and as a percentage of CS activity. Muscle enzyme studies showed low complex III and IV (26 and 27% of control respectively, 52% relative to CS). This result is considered consistent with but not diagnostic of a respiratory chain defect. In contrast, liver enzyme studies showed a normal complex III level (13.3 /min/mg; normal range 9-14) and a high complex IV level (3.4 /min/mg; normal range 1.1-1.6). None of the common mitochondrial DNA mutations (nt 3243 A to G, nt 8344 A to G, nt 8993 T to

Table 1 Results of investigations on the patients

Investigation	Patient 1	Patient 2	Patient 3
Karyotype	46,XY	46,XY	46,XY
Urine amino acids	nd	Normal	Slightly raised pipercolic acid
Urine organic acids	nd	Raised lactate, 4 hydroxyphenyllactate, 4-hydroxypropyruvate	Raised 4-hydroxyphenyllactic and 4-hydroxyphenylpyruvic acids
Respiratory chain enzymes in liver	nd	Raised complex IV	nd
Respiratory chain enzymes in muscle	nd	Decreased complex III, IV	Decreased complex III, IV
Total carnitine (35–65)	nd	43	12
Free carnitine (30–60)	nd	20	8
Mitochondrial DNA	nd	No mutation detected	No mutation detected
Lactate maximum mmol/l (1.0–1.8)	nd	23.5	3.0
Very long chain fatty acids	nd	Normal	Normal
Plasma amino acids	nd	Normal	nd
White cell count maximum 10 ⁹ /l (4–11)	2.3	21.9	94.7
AST U/l (20–80)	nd	172	146
Total protein g/l (50–71)	nd	51	83
Albumin g/l (29–45)	nd	38	43
Bilirubin conjugated µmol/l	80	167	79
Blood ammonia maximum µmol/l (<50)	nd	364	41
Triglycerides mmol/l (0.9–2.0)	nd	nd	3.3
Cholesterol mmol/l (<4.5)	nd	nd	5.4

nd: not done.

G, nt 8993 T to C) were present in lymphocytes or muscle.

Patient 3 had an identical appearance to his brother. His birth weight was 2360 g (5th centile), length 43.5 cm (<3rd centile), and OFC 34.5 cm (50th centile). He also had a grossly distended abdomen and a thickened bladder wall was visualised on ultrasonography. A suction rectal biopsy showed ganglion cells, excluding Hirschsprung disease. He developed necrotising enterocolitis which was managed conservatively with intravenous nutrition, antibiotics, and nasogastric suction and drainage. Patient 3's phenotype evolved with time. Over a period of weeks he developed a progeroid appearance with deeply set eyes, prominent cheeks, and relative enlargement of the cranium, and marked reduction of subcutaneous fat with prominent superficial veins was seen throughout including on the buttocks. There were no abnormal fatty deposits. The skin was

translucent and thin in appearance and texture. There was no evidence of neurodevelopmental progress.

A muscle biopsy done in life showed no diagnostic abnormality and in particular there were no changes suggesting mitochondrial pathology, such as ragged red fibres or absence of cytochrome C oxidase (COX) staining.

He died aged 75 days. Necropsy identified similar pathology of the gastrointestinal and urogenital tracts to his brother. Changes of necrotising enterocolitis were present with no evidence of perforation or stricture. The liver histology was markedly abnormal with cholestatic hepatitis with expanded portal tracts containing a proliferation of bile ductules. Early portal tract to portal tract bridging by fibrous tissue containing proliferated bile ductules was noted. The extrahepatic biliary tree was normal. The neuropathology was essentially normal. Skeletal x rays done post mortem did not show any significant features.

The results of the investigations on the patients are shown in table 1.

Table 2 Comparison of the clinical features in the patients described with those seen in Wiedemann–Rautenstrauch syndrome

Clinical sign	Cases presented	Wiedemann–Rautenstrauch syndrome
Survival	All dead by 75 days	Prolonged survival recorded
IUGR	Yes	Yes
Postnatal growth retardation	Severe	Yes
Neurodevelopmental progress	None seen in longest survivor	Developmental delay in most cases
Sex	All male	Male and female
Pseudohydrocephalus	No	Yes
Fontanelles	Wide anterior	Wide anterior, delayed closure
Prominent scalp veins	Yes	Yes
Hair	Low anterior hair line	Sparse
Progeroid face	Yes	Yes
Eyes	Deep set	Deep set
Nose	Very small	Small, beaked
Mouth	Small	Small
Natal teeth	No	Yes
Jaw	Micrognathia	Prominent
Lipoatrophy	Yes	Yes
Sacral fat accumulation	No	May occur with time
Sudanophilic leucodystrophy	No	Yes
Pseudo-obstruction of GIT, GUT	Yes	No
Liver dysfunction	Yes	No
Inheritance	?X linked, ?mitochondrial	Autosomal recessive

IUGR: intrauterine growth retardation, GIT: gastrointestinal tract, GUT: genitourinary tract.

Discussion

Clearly the three males in this family have the same condition. This association of features has not been previously described.

A number of neonatal progeroid syndromes have been reported. The best known of these is the Wiedemann–Rautenstrauch neonatal progeroid syndrome.^{2–4} In this syndrome the typical progeroid appearance is associated with a prominent jaw and natal teeth. By contrast, the patients we presented had micrognathia and natal teeth were absent. The prominent gastrointestinal and urinary tract features of our cases are not featured in the reports of Wiedemann–Rautenstrauch syndrome which is autosomal recessive.⁵ There have been reports of sudanophilic leucodystrophy in Wiedemann–Rautenstrauch syndrome.^{6,7} This was not the case in our patients. Table 2 compares this syndrome with the patients presented.

Hagadorn *et al*⁸ reported a girl with features of a neonatal progeroid syndrome with abdominal distension and vesicoureteric reflux. She differed from the cases we have described in that her gastrointestinal distension resolved with nasogastric feeding and urinary tract dilatation was limited to the renal pelvices. Their patient had hypercalciuria and renal parenchymal calcification. Hypercalciuria was also seen in the patient reported by Bitoun *et al*⁹ but was not looked for in our patients.

The family described by de Martinville *et al*¹⁰ shows some features similar to the cases in this report. Male monozygotic twins with a neonatal progeroid syndrome were presented. An older sib with dysmorphic features died at 50 days. There are no details of the child's sex or clinical features other than talipes equinovarus. The children's mother also had two miscarriages. One twin died at 10 minutes and details are limited regarding its ante- and postmortem features. This child is said to have had the same dysmorphic features as his twin brother which included typical progeroid features as well as micrognathia, sparse hair, eyelashes, and eyebrows, hypoplastic finger nails and absent nails on the fifth finger bilaterally, camptodactyly, and no natal teeth. The longer surviving twin had gastrointestinal problems, the exact nature of which were not reported apart from severe failure to thrive. Significant changes were present in the skin and its appendages. He died at 6 months. Necropsy was not performed. It is possible that these three sibs had the same condition as the patients we describe, but there are some differences between the cases. The patients of de Martinville *et al*¹⁰ had prominent digital changes and there was no description of urinary or gastrointestinal pseudo-obstruction.

The pattern in our family is strongly suggestive of inheritance through the maternal line. Neither a mitochondrial nor an X linked neonatal progeroid syndrome has previously been described.

In view of the prominence of gastrointestinal and genitourinary pseudo-obstruction in our patients, we reviewed other conditions in which such features are mentioned. Intestinal pseudo-obstruction is seen in a number of conditions. Myoneurogastrointestinal encephalopathy syndrome (MNGIE) has pseudo-obstruction as one of its features and in some cases results from mitochondrial DNA deletions.¹¹ This condition has not been seen in neonates. An X linked form of intestinal pseudo-obstruction has recently been mapped to Xq28,¹² but here specific histological abnormalities are present in the bowel. These were not specifically looked for in our cases but there was no pyloric stenosis, malrotation, or short gut. Harris *et al*¹³ reported brothers with intestinal pseudo-obstruction and natal teeth who both died before 6 months. No mention of urinary tract dilatation or progeroid features was made and the relevance to our cases is unclear but is of interest given the presence of natal teeth in Wiedemann-Rautenstrauch syndrome.

A mitochondrial aetiology is possible with the maternal inheritance pattern observed in the cases described. The results of mitochon-

drial investigations have not given convincing evidence for a mitochondrial cause, however. Although inconsistency in respiratory chain enzyme activities between tissues is often observed in respiratory chain disorders, the abnormal levels are usually observed in the clinically affected organ. In this case, complex III activity was normal in the liver, yet liver function was abnormal, but reduced in muscle, and complex IV was raised in the liver of patient 2. The results cannot be regarded as diagnostic and are at best consistent with primary mitochondrial pathology.

An X linked recessive aetiology would also be consistent with the inheritance pattern observed. It is possible that a mutation in a gene on the X chromosome, which encodes for a protein involved in the respiratory chain, is present. None of the subunits encoding respiratory chain enzymes is known to reside on the X chromosome; however, many nuclear encoded genes are yet to be mapped.¹⁴ Complex III contains 11 polypeptide subunits, 10 of which are nuclear encoded, the other being encoded by a mitochondrial DNA gene. Complex IV is composed of 13 polypeptide subunits of which three are mitochondrially encoded and the remainder nuclear.¹⁴

An alternative mechanism is that there is a gene locus on the X chromosome which has an effect on the mitochondrial genome. The first report of linkage for a nuclear gene predisposing to mitochondrial deletions has recently been published.¹⁵

In conclusion, we have presented a neonatal progeroid syndrome with pseudo-obstruction of the urinary and gastrointestinal tracts affecting monozygous twin boys and their maternal uncle. Their features differ significantly from any cases previously described. These patients add weight to the proposition of Hagadorn *et al*⁸ that there is clinical heterogeneity among conditions diagnosed as a "neonatal progeroid syndrome".

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