Leber's congenital amaurosis—a new syndrome with a cardiomyopathy

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SUMMARY Seven members of four families had nystagmus noted by 4 months of age, poor vision, photophobia, and a markedly reduced or absent electroretinogram. Six of these patients had a life threatening episode of cardiac failure in infancy. There were also two neonatal deaths, and one of the affected children died at 2 years and one at 19 years. The five surviving children are well, remain with nystagmus, and have visual acuities of less than 6/60, with the eldest two having lost perception of light. They have a short obese habitus distinct from that of their unaffected siblings and parents.

Leber's congenital amaurosis (LCA) is a heterogeneous group of conditions having in common the features originally described by Leber in 1869.² Leber noted reduced vision before the age of 1 year, nystagmus, and poor pupillary reactions with the eventual appearance of degenerative changes in the fundi. The inheritance is thought to be autosomal recessive.³⁴ Leber subdivided the condition in 1916 into a simple ocular form and one combined with mental retardation.⁶ In 1954 Franceschetti and Dieterle noted the markedly reduced or absent electroretinogram (ERG).⁷ The criteria for the diagnosis are now: a profound visual defect from birth, a markedly reduced or absent ERG, and a normal fundal appearance or a retinal dystrophy.

Specific disorders such as infantile or late Batten's disease (neuronal ceroid lipofuscinosis),⁸ peroxisomal disorders (such as Zellweger syndrome⁹ and infantile Refsum's disease¹⁰), and mitochondrial cytopathy¹¹ need exclusion, but their difference from LCA is usually clinically evident. There may be cases of cone dysfunction syndromes or congenital stationary night blindness¹² within any group of patients initially diagnosed as LCA, in particular among those with relatively preserved vision. Appropriate electrophysiological studies will exclude these but should be repeated.

The commonest fundus abnormality in LCA is thinning of the retinal arterioles and a granular retinal pigment epithelium.¹³ The appearance of the fundus has also been normal,¹³¹⁴ or shown macular 'colobomas',¹⁵ peripheral white dots,¹⁴ nummular pigmentation,¹⁶ granular macular pigmentation, and

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**Fig. 1 Pedigrees.**

- **1**
  - I
  - II
  - A

- **2**
  - I
  - II
  - B

- **3**
  - I
  - II

- **4**
  - I
  - II

- **Symbols**
  - □ Probably affected
  - □ Normal male
  - ○ Normal female

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pseudopapilloedema. Cataracts and keratoconus and hypermetropia may be found, and LCA has been described in association with a saccade palsy; this may be a variant of Joubert's syndrome with retinal dystrophy.

The systemic associations described include mental retardation, seizures, deafness, EEG anomalies, CT scan changes, and renal abnormalities, which may be associated with skeletal malformation or endocrine dysfunction, suggesting a multisystem disorder. There is still value in keeping these patients within the LCA classification, as their initial presentation with an uncomplicated ocular problem does not permit differentiation from classical LCA. In some family members renal function may remain normal unless it is severely stressed, as by an episode of dehydration. In all studies reporting systemic abnormalities, their incidence is probably influenced by the referral pattern.

We now report the association of LCA with acute cardiac decompensation in infancy, which appears to carry a good long-term prognosis for the survivors. We describe seven cases from four families.

Case reports

Case 2.112
This is the second daughter of normal parents. Her elder sister is also healthy. At 3 months of age nystagmus was noted and poor vision suspected. At 7 months while attending hospital for investigation she collapsed with severe cardiac failure due to a cardiomyopathy (possibly viral), which responded to medical therapy. Viral antibody titres were normal and no congenital structural or vascular cardiac abnormalities were found.

There were +9.00 dioptres of hypermetropia, narrow retinal arterioles, and absent electroretinograms (ERGs) from both eyes. At aged 2½ years she was well on digoxin and diuretics, and echocardiography showed improvement in left ventricular performance. Paradoxical pupil responses were noted. Aged 3 years she can identify the 6/60 letter at 2 metres binocularly. Off all medication, her exercise ability is limited only by visual handicap. Cross-sectional echocardiography shows mild dilatation of the left ventricle, with a shortening fraction of 39%. The electrocardiogram shows minor abnormalities of the repolarisation phase. Intellectual achievement is as yet uncertain, but development may be delayed even for a visually handicapped child. Her height is on the 90th centile, but her parents are tall. Her weight at 24 kg is far above the 97th centile.

Case 2.111
This, the first born male child of normal parents, died suddenly aged 3 weeks. Necropsy showed pulmonary valve stenosis, left ventricular subendocardial fibrosis, a patent ductus arteriosus, and anomalous systemic venous drainage.
26%. His height is 123 cm (below the 50th centile) and weight 40 kg (above the 97th centile).

CASE 3.11 1
This, the first born female child of normal parents, died at age 9 weeks. The original diagnosis was renal failure, but death may have been due to cardiac failure. Her eyes had made 'fluttering' movements and she disliked sunlight.

CASE 3.11 3
The brother of case 3.11 1, he collapsed at age 4 months owing to cardiac failure secondary to cardiomyopathy. This responded to medical treatment. At 6 months nystagmus and photophobia were noted. At 3½ years he seemed to see well but sat close to the television. Paradoxical pupil responses were noted on clinical examination. The retinal arterioles were narrow and there was a sheen round the fovea. The flash ERG was undetectable, and the flash VER was greatly reduced in amplitude. At 5 years his unaided visual acuity was 2/36 for each eye and N18. He could name primary colours correctly. There was +8·00 dioptres of hypermetropia in each eye. The retinal arterioles were narrow, but there was no abnormal retinal pigmentation. His visual fields appeared constricted. He attends a school for the handicapped; his IQ is 79 as assessed on the British Ability Scale, WPPSI, and Merrill-Palmer. At aged 5 years there is no evidence of cardiac failure. His electrocardiogram shows a low-voltage trace for a child but is otherwise normal. His cross-sectional echocardiogram shows only that the left ventricle is at the upper limit of normal dimensions, with a shortening fraction of 35% and a slight increase in ventricular wall thickness. His height is 100·8 cm (on the 3rd centile) and weight 23·5 kg (above the 90th centile).

CASE 3.11 4
The sister of cases 3.11 1 and 3.11 3, she was also photophobic and had nystagmus and poor vision; she died from cardiac failure at 2 years. Post-mortem examination showed abnormalities throughout the skeletal muscle, with considerable variation in fibre size. The heart muscle showed swollen hypertrophic nuclei, with fibre variation and large eosinophilic fibres consistent with a dystrophy. The brain showed some neuronal cortical degeneration. Retinal histology failed to show a differentiated macular region and poor definition of the outer plexiform layer, and the photoreceptor outer segments were slightly stunted. The retinal pigment epithelium particularly near the posterior pole and in the peripapillary region was distinctly hypomelanised.
CASE 4.II 1
A male child was stillborn at 6 months gestation, with birth weight 625 g. The mother was suffering from pre-eclampsia.

CASE 4. II 2
The birth of this girl was induced at 35 weeks gestation because of maternal hypertension. Her birth weight was 2443 g and development was normal until 6 months of age, when nystagmus and photophobia were noted. She learned to read large print books, but by 9 years of age she had lost perception of light. At 10 years the ERG was absent. There were roving eye movements, 5 dioptres of hypermetropia, pale optic discs, and attenuated retinal vessels, with perifoveal and equatorial pigmentation. At age 28 years there are posterior lens opacities. The fundus now has diffuse clumps of pigmentation and pigment epithelial atrophy. There have been no episodes of heart failure. Cardiovascular clinical examination, ECG, and echocardiogram gave normal results. Her weight is 70 kg and height 147.5 cm (her mother is 152 cm and father 178 cm).

CASE 4.II 3
This was the brother of 4.II 2. His birth was induced because of maternal hypertension at 32 weeks, and he weighed 1363 g. At 2 months he was floppy and had poor vision and by 4 months had difficulty in breathing owing to myocarditis or endocardial fibroelastosis. He had several episodes of cardiac failure, only partially controlled with digitalis. At 10 years he was photophobic, with visual acuities of 3/60 right, 2/60 left, and N18 held very close. There were pendular nystagmus, a sluggish pupil response, and normal optic discs but narrowed retinal vessels. There was no recordable ERG. His vision was no perception of light by his teens, and he died of heart failure at 19 years. He was never obese despite being wheelchair bound from 14 years.

FURTHER INVESTIGATIONS
Other tests performed on cases 2.II 2, 2.II 3, and 3.II 3 that failed to show any significant abnormality were: full blood profile (no vacuolated lymphocytes were seen), plasma urea, electrolytes and liver function tests, plasma bile acids and very long chain fatty acids, serum phytanic acid, and chromosome analysis (including G banding).

Discussion
With the passage of time the disease that Leber initially described has become more complex as more of these rare cases are grouped and documented. It appears that within the broad group of LCA lie various subgroups. Some are clearly defined: those with mental retardation, with renal disease, which may overlap with Senior’s syndrome, with a saccade defect, and with a variety of fundus defects. It is not yet clear whether these cases are genetically distinct or what is their visual prognosis.

The syndrome that we describe is probably a genetically distinct subset of Leber’s congenital amaurosis featuring a profound and progressive visual defect with a severely reduced electroretinogram, and cardiac failure with reduction in left ventricular function appearing acutely in infancy. Although the visual prognosis is very poor, if the
patient survives the acute cardiac decompensation
the prognosis for life appears to be good, though the
left ventricle does not recover fully.

The above cases emphasise the need for a general
examination in cases of LCA. Case 1.II 2 became
severely ill while under investigation for poor vision.
The association between LCA and renal abnor-
malities is already well known, but this important
association of cardiac failure with apparently classical
ocular features of LCA has not been reported
previously. In three cases the visual failure has
progressed to no perception of light, which is unusual
in LCA.

The surviving children are all obese, but this may
reflect reduced exercise owing to their visual handi-
cap. Four are short; three below the 10th centile, one
just above the 25th centile. The fifth child (case 1.II
2) is on the 90th centile for height but she comes from
a tall family and her weight exceeds the 97th centile.
A particular habitus may be part of this condition.
The affected individuals, as their parents spontane-
ously commented when they met, look more similar
to each other than to their normal siblings or parents.

Muscle biopsy has not been considered justifiable
in most cases, but in the two cases examined at post-
mortem features of a mitochondrial myopathy were
not seen. An enzymatic defect has not as yet been
identified. Evidence for a peroxisomal defect was
sought by measurements of plasma bile acids, very
long chain fatty acids, and phytanic acid. There are
few reports of ocular histology in LCA, and we report
our cases with the caution in that this may not be
typical of classical LCA.

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