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 conditions¹ 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.^{3,5} 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.³ The appearance of the fundus has also been normal,^{13,14} or shown macular 'colobomas',¹⁵ peripheral white dots,¹⁴ nummular pigmentation,¹⁶ granular macular pigmentation, and

Fig. 1 Pedigrees.

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pseudopapilloedema.¹⁷ Cataracts and keratoconus¹ and hypermetropia may be found, and LCA has been described in association with a saccade palsy¹⁸; this may be a variant of Joubert's syndrome with retinal dystrophy.¹⁹

The systemic associations described include mental retardation,^{3-5 20-22} seizures,²² deafness,²³ EEG anomalies,^{3 21} CT scan changes,²⁰ and renal abnormalities,^{24 25} which may be associated with skeletal malformation²⁶ or endocrine dysfunction,²⁷ 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 1. II 2

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. II 1

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.

CASE 2. II 2

The sister of case 2. II 1, she developed cardiac failure at 3 weeks of age. Cardiac catheterisation showed an enlarged heart with raised pulmonary artery pressure and end-diastolic pressures in both ventricles. There was a left to right shunt through a patent foramen ovale. The cardiac failure responded to medical therapy. As she was ill in early infancy, little visual responsiveness was expected. Nystagmus was noted at 4½ months, she was photophobic, and poked or rubbed her eyes. At 8 years her binocular acuity was 3/60 and N18, and she had poor colour vision. By 14 years she has no perception of light, a marked ptosis with poor lid creases, and nystagmus. The pupils are mid-dilated and do not respond to light. There is a posterior lens opacity. Retinoscopy measurements are: right +5.00/+1.00 at 90° and left +5.50/+1.00 at 90°. There are pale optic discs, narrow retinal arterioles, thin retinal pigment epithelium and some pigment clumping.

No ERGs or visually evoked responses (VERs) were detectable. The visual handicap limits her full effort potential, but there is no evidence of cardiac failure. The electrocardiogram shows sinus rhythm with a mild intraventricular conduction delay. Cross-sectional echocardiography shows only that the left ventricle is dilated, with the shortening fraction being only 18%. Her height is 100.8 cm (on the 3rd centile) and weight 23.5 kg (above the 90th centile).

CASE 2. II 3

The brother of cases 2. II 1 and 2. II 2, he presented at aged 6 weeks with cardiac failure which responded to therapy. Nystagmus was noted at 4 months, but he had smiled to a face by 2 months of age, and a visual defect was only suspected at 1 year. He was photophobic, and at 22 months paradoxical pupil responses were noted. The ERG from each eye was of small amplitude, and the flash VERs were markedly attenuated and degraded.

At 8 years of age his corrected visual acuity is 3/60 right, 4/60 left, and N14 at 4 inches (10 cm). He had defective colour vision, identifying only the control plate of the Ishihara series. The optic discs are pale, with narrow retinal arterioles but no pigment clumping. Retinoscopy is +7.00 dioptres sphere right, +7.50 dioptres sphere left. He is well without any medication, and in sinus rhythm with mild ST wave changes anteriorly on the electrocardiogram. Cross-sectional echocardiography shows only that the left ventricle is dilated, the shortening fraction being

Fig. 2 Echocardiogram from case 2.II 3 (markers at 1 cm intervals). a: Long axis parasternal view of left ventricle in early systole. The ventricle is very dilated and the wall is not thickened. b: m Mode scan demonstrates an end diastolic dimension (EDD) of 5.4 cm, and an end systolic dimension (ESD) of 3.6 cm (normal range for BSA EDD: 2.7–4.9 cm, ESD 1.7–3.2 cm). LV=left ventricle. LA=left atrium. Ao=aorta. IVS=interventricular septum. PVW=posterior ventricular wall.

26%. His height is 123 cm (below the 50th centile) and weight 40 kg (above the 97th centile).

CASE 3. II 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. II 3

The brother of case 3.II 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. II 4

The sister of cases 3.II 1 and 3.II 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.

Fig. 3 Ocular histology of case 3.II 4. Histology of the peripapillary retina shows a prominent nerve fibre layer and a well-defined inner plexiform layer. The outer plexiform layer, however, is almost non-existent. Photoreceptor outer segments, including both rods and cones, are seen, though their development appears to be stunted. The melanin content of the pigment epithelium is markedly reduced. Haematoxylin and eosin, $\times 340$.

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 fibro-elastosis. 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 abnormalities 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 handicap. 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 spontaneously 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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