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Neurological abnormalities in congenital amaurosis of Leber

Review of 30 cases

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SUMMARY A retrospective study was made of 30 children with Leber's amaurosis (congenital retinal blindness). 24 presented with severe visual impairment, typical ophthalmological findings, and absent electroretinograms. 6 other children, though presenting with marked visual loss and absent electroretinograms were later shown to be less severely affected. Some of the more severely affected children had associated neurodevelopmental or renal abnormalities.

Leber's amaurosis, or congenital retinal blindness, sometimes also known as infantile tapetoretinal degeneration, was one of several ophthalmological diseases described by Leber (1869) towards the end of the last century.† Two large surveys have been made of the disease, one in Sweden (Alström and Olson, 1957), and the other in the Netherlands (Schappert-Kimmijser *et al.*, 1959). In the Swedish series, neurological abnormalities were not thought to be significantly more frequent than in the general population, but the survey largely depended on children from a school for mentally normal blind children and was thus biased against neurodevelopmental abnormality. In the Dutch study it was concluded that the incidence of neuropsychiatric disorders was higher than in the general population, but these disorders were not described in detail.

Recently there have been reports of an association between Leber's amaurosis and neurological abnormalities (Dekaban and Carr, 1966; Dekaban, 1969a, b, 1972). A retrospective study was therefore made of all children diagnosed as suffering from Leber's amaurosis at The Hospital for Sick Children, London, between 1968 and 1973.

Patients

Diagnosis of Leber's amaurosis was based on the following criteria. (1) Blindness or severe visual impairment during the first 6 months of life. (2) Absence or marked reduction of the electroretinogram (ERG). (3) Normal, or near normal appearance of the fundus with, at most, mild pigmentary changes.

These criteria allowed exclusion of blindness due to other local causes such as retrolental fibroplasia, congenital cataract, septo-optic dysplasia, and achromatopsia, and also blindness due to cortical defects (cortical blindness) and severe mental subnormality.

There were 30 children who fulfilled these criteria and 4 others in whom the diagnosis had originally been seriously considered but later rejected. 2 of these patients were achromats, and 2 suffered from complex degenerative neurological diseases, which were complicated by tapetoretinal degeneration early, but not severely.

The 30 patients fell into two main groups depending on the severity of visual impairment. In the main group of 24 patients there was severe and permanent blindness. In the second group, though expert opinion in early infancy asserted that visual loss was severe as judged by poor or absent fixation and roving eye movements, an opinion apparently supported by an abnormal ERG, follow-up showed visual acuity far superior to that considered to be characteristic of Leber's amaurosis. This matter will be considered in greater detail later. We propose therefore to identify two groups with either severe or relatively mild involvement.

Severe form of amaurosis

There were 12 boys and 12 girls, representing 22 families. There were two sibships with more than one affected child, and 4 examples of parental

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†This condition is in no way similar to Leber's hereditary optic atrophy which leads to sudden visual loss usually in young males due to optic nerve disease.

consanguinity. 21 families were of European origin while the remaining parents were first cousins from the Sudan.

No useful vision was detected in any patient, and examination showed roving eye movements and poor pupillary response to light. Some degree of enophthalmos was usually present and ocular manipulation was common. Ophthalmological examination in young infants was usually reported as normal, but occasionally slight accentuation of pigmentation in an equatorial distribution, with retinal arterial attenuation, was mentioned. Above one year of age, retinal arterial attenuation was invariably recorded, with concomitant increase of granular pigmentation equatorially, diffusely, or concentrated at the macula. The occurrence of pigmentation in the macular areas in Leber's amaurosis is important in distinguishing this condition from tapetoretinal degeneration of later onset (retinitis pigmentosa) in which macular pigmentation is extremely rare. The optic discs were not recognized to be atrophic until after the first year, and then only in 5 patients whose ages ranged from 12 months to 10 years.

ERG was absent in all cases at the earliest examination. Evoked cortical responses were reduced or absent in 5 out of the 12 infants who were appropriately tested.

Renal abnormalities. Intravenous pyelograms were abnormal in 2 out of 8 patients examined. In one severely subnormal patient only one kidney was shown while another severely subnormal and deaf child had horseshoe kidneys.

Mental development and neurological status. Mental status could be defined in 21 patients and 11 were found to be moderately or severely mentally subnormal, with variable hypotonia. The severely subnormal, hypotonic child with a horseshoe kidney mentioned above also had severe balancing problems and was presumed to have a cerebellar deficit, as well as a high tone sensorineural hearing loss. The latter may have been the consequence of moderately severe and unexplained jaundice in the newborn period, when the nonconjugated bilirubin level rose to 18 mg/100 ml (308 μmol/l) on the fourth day. Though the liver in this patient was easily palpable and firm subsequently, transaminase levels were consistently normal, and he was never again jaundiced. Air encephalography at 5 months showed moderate dilatation of the lateral ventricles with more marked enlargement of the temporal horns. In the region of the superior medullary velum there was a slightly lobulated indentation of the fourth ventricle. When repeated at 10 months, the fourth ventricle appeared normal, but the third and lateral ventricles were more enlarged, suggesting atrophy. There was a filling defect suggestive of a cyst in the chiasmatic cistern. He died suddenly and unaccountably at 5½ years without preterminal evidence of either renal dysfunction or progressive neurological disease.

Air encephalography by the lumbar route was performed in 8 of the other mentally subnormal infants and abnormalities were defined in 7. These comprised mild ventricular dilatation and widening of the cerebral sulci in 6, irregularities in outline of the chiasm or optic nerves (2 cases), enlargement of the interpeduncular and chiasmatic cisterns (2 cases), enlargement of the cisterna magna (3 cases), and cerebellar atrophy (3 cases). Air encephalography in 2 mentally normal children was unremarkable. There was only one family in which there was a sib with uncomplicated blindness, and one who was mentally handicapped as well as blind. In the other sibship with more than one affected child, both were mentally normal.

Mild form of amaurosis

Although as judged by the early presentation of visual handicap and the reduction or absence of an ERG response in the first year, certain children should be considered alongside those already described, it seems appropriate to consider as a separate group 4 girls and 2 boys whose visual handicap was obvious before 6 months of age, and in whom the ERG response was reduced or absent. Follow-up invariably showed that their visual handicap was much less severe than originally suspected.

In 5 children old enough to obtain reliable estimates, corrected visual acuities were 6/60 at 5 years, 6/24 at 5 years, 6/12 at 6 years, 6/9 at 10 years, and 4/36 at 8 years respectively. In 2 of the children who were photophobic, visual competence was much better in poorly illuminated conditions and they benefited from dark glasses. In none of these children was there any hint of visual deterioration—symptomatically the reverse was true. One of the children was severely mentally handicapped, but mental development in the others seemed normal. No neurological deficits were observed. Neither pyelography nor air encephalography was performed.

Discussion

Refinements in electrodiagnostic techniques now enable more accurate diagnosis of congenital blindness. Thus congenital retinal disorders may be differentiated from other causes of blindness, such

as septo-optic dysplasia or retrochiasmal disease. Computerized averaging techniques with flash allow assessment of the illuminated electrical response from the retina (ERG) using noncorneal electrodes so that examination can be performed without anaesthesia and the evoked cortical response (VER) can also be recorded by a similar technique (Harden, 1974). This method was used in many of our cases, though in others the ERG was recorded with corneal electrodes under general anaesthetic. ERGs recorded by the two techniques correlate closely. The apparent discordance between ERG and VER in several patients, especially those with the milder forms of the disease that we describe is not unique and is seen in a number of circumstances. (1) Delayed development of ERG (Harden, 1974). (2) Small area of retained central visual field. (3) Neuronal ceroid lipofuscinosis, also known as Batten's disease and amaurotic family idiocy (Harden *et al.*, 1973).

It has been suggested that in most children the ERG normally develops up to the age of 1 year (François and Rouck, 1968), but in others the ERG may remain small for even longer periods (Harden, 1974). Thus in young children the development of the ERG may be delayed and this may account for some of the children in our group who subsequently displayed moderately good visual acuity.

Preservation of a few degrees of central vision may produce a minimal or flat ERG in the presence of an adequate VER and this is also consistent with the known retinocortical magnification factor (Daniel and Whitteridge, 1961). Finally in certain retinocerebral degenerations, namely Batten's disease, an absent ERG may be associated with an enhanced VER. The neurophysiological explanation for these inconsistent responses has not yet been elucidated (Harden *et al.*, 1973). Combination of these several factors may account for the apparent discrepancy seen especially in these 5 children who had absent ERGs initially but who were found subsequently to have varying degrees of retinal central vision. The varying electrical response corresponds with the findings of Henkes and Verduin (1963) who subdivided Leber's amaurosis according to differing electro-oculographic responses. Inevitably, however, there must be uncertainty about the genetic relationship between the forms which we distinguish as severe and mild, though they are both probably inherited as autosomal recessive conditions. In common with other recessively inherited degenerative disorders there is probably an underlying metabolic abnormality; further genetic discrimination between different forms of disease must depend on a precise definition of presumed enzymic abnormalities.

Similar considerations apply to the discussion of complex neurodevelopmental abnormalities associated with severe congenital retinal blindness. Disequilibrium, hypotonia, severe subnormality, and in one case severe sensorineural hearing loss point to a diffuse encephalopathic process which has been described previously (Dekaban, 1969a, 1972). The strongest justification for regarding patients thus affected as representing phenotypic variants is the existence of families (including our family, and that of Dekaban and Carr, 1966) in which neurodevelopmental abnormalities exist in some but not all of the sibs who are blind, and it is unlikely that this is a chance association. Likewise the association with renal disease, which has frequently been described (Löken *et al.*, 1961; Senior *et al.*, 1961; Dekaban, 1969a, b) but was not so striking in our series. The two abnormalities discovered in our patient, a horseshoe kidney and a nonfunctioning right kidney, have not been described previously in association with Leber's amaurosis. Renal dysgenesis, renal medullary cystic disease or polycystic disease, which is apparently common in older patients with Leber's amaurosis and is also associated with other forms of tapetoretinal degeneration (Fairley *et al.*, 1963; Meier and Hess, 1965; Herdman *et al.*, 1967; Schmike, 1969; Mainzer *et al.*, 1970; Hussels, 1971; Betts and Forrest-Hay, 1973; Abraham *et al.*, 1974), were not recognized in our patients, but may have been overlooked because systematic and extensive renal investigations were not undertaken.

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