A syndrome of congenital retinal dystrophy and saccade palsy—a subset of Leber's amaurosis

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SUMMARY Three children who presented in infancy with a severe visual defect and absent or barely recordable electroretinograms, with relatively well preserved visually evoked cortical potentials, were subsequently found to have vertical and horizontal saccade palsies with head thrusts but relatively good visual acuity. These children, who were clearly different from other infants with congenital retinal dystrophy, were also developmentally delayed and had systemic motor and speech defects, but their visual prognosis was relatively good. The recognition of their saccade palsy was delayed because their poor visual attention in infancy was ascribed purely to the tapetoretinal degeneration. We consider these patients represent a clear subset of those patients who are diagnosed as having congenital retinal dystrophy or Leber's amaurosis.

Congenital retinal blindness (Leber's amaurosis), which is a common cause of blindness in children, is an inherited retinal dystrophy of variable severity. Between 10% and 18% of children in institutions for the blind suffer from this condition, which is thought to be autosomal recessive in its inheritance.^{1,2} The usual presentation is with suspected blindness or poor vision with nystagmus from birth or in the first few months of life. There may be photophobia, and eye poking (digito-ocular sign of Franceschetti)³ is sometimes seen. There is usually nystagmus or roving eye movements, and the pupil reactions may be sluggish or absent. The fundus is often normal or subtly abnormal when the child is examined in the first few months of life, but later a variety of abnormal fundus appearances may be seen. The fundus is often albinotic; there may be a diffusely granular appearance to the retinal pigment epithelium, and white punctate spots are sometimes seen in the periphery.⁴ There may be a scattered pigmentary change, retinal arteriolar narrowing, and pallor of the optic discs. In some older patients the fundus may resemble that in typical retinitis pigmentosa. The appearance of optic disc oedema⁵ and 'macular colobomas'^{6,7} has also been reported, and affected children are often hypermetropic. The diagnosis of congenital retinal dystrophy is made by the finding of an absent or markedly reduced electroretinogram (ERG) in a child with blindness or poor vision and nystagmus from birth or

in the first few months of life. Other ocular abnormalities such as enophthalmos, keratoconus, and cataract are often seen in older children.

Congenital retinal blindness (CRB) has been reported in association with various systemic conditions. Mental subnormality, psychiatric disturbance, neurodevelopmental disorders, and certain structural abnormalities of the central nervous system (CNS) are said to be commoner in this condition than in the general population. The incidence of these abnormalities in CRB is, however, difficult to determine because of the differences in patient selection in different studies and also because of the different referral patterns to the various centres. Alström and Olson¹ in a large series from Sweden found no association with neurological disorders, but their cases were drawn from a school for mentally normal blind children, and therefore their results were biased against neurological or psychiatric disorder. Schappert-Kimmijser *et al.*² found major neurological and psychiatric abnormalities in 25% of affected children in a large study from Holland. Other smaller studies^{4,8-11} have found a higher incidence of such abnormalities, but again this may reflect a bias in selection. Vaizey *et al.*,⁸ for instance, base their study on patients referred to a national paediatric neurological centre. Two recent reports^{12,13} found no major increase in the incidence of subnormality or neurological disorder in this condition. Although specific structural abnormalities of the CNS are

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uncommon in CRB, there appears to be a definite association with hypoplasia of the cerebellum.^{8 12 14} Nickel and Hoyt¹² reported the results of CT scanning in 31 patients with CRB. A structural defect of the CNS was found in only three cases, and in each case the lesion was hypoplasia of the cerebellar vermis. Dekaban¹⁴ found hypoplasia of the cerebellar vermis

condition, or there are separately inherited diseases accounting for the variation.

Congenital retinal blindness is therefore seen in association with several systemic disorders. We report three cases in which a congenital retinal dystrophy is associated with an ocular motor disorder similar to ocular motor apraxia.

Fig. 1a

Fig. 1b

and immature cortical neurons at post-mortem examination of a 3-year-old boy with CRB.

Childhood retinal dystrophies have also been reported in association with renal abnormalities.^{8 14-22} Senior and others¹⁵ and Loken and others¹⁶ independently first described the association of a recessively inherited renal dysplasia, juvenile nephronophthisis, or medullary cystic disease and a tapetoretinal degeneration indistinguishable from Leber's amaurosis. The renal and retinal abnormalities have also been described in association with another recessively inherited condition—congenital hepatic fibrosis.²³

Various authors have reported great variations in the level of vision in CRB. All of Nickel and Hoyt's¹² 31 patients had vision estimated at the level of light perception or worse. Other authors^{1 2 8 11 13} have reported a small group of children who have reasonably good central vision when old enough to be formally tested, despite apparent blindness and a reduced or absent ERG in infancy. This relatively high level of acuity has been attributed to preserved central visual function, with widespread peripheral retinal abnormalities accounting for a reduced ERG. Clearly there is either great heterogeneity within one

Fig. 1c

Figs. 1a,b The right fundus of case 1 at 22 months shows the very slightly pale right optic disc and its macula. The arterioles were probably within normal limits. c: Case 1: the fluorescein angiogram was normal.

Case reports

CASE 1

This boy was the first child of healthy, unrelated parents. His mother received several courses of

ampicillin in pregnancy, for recurrent parotid swelling, but the pregnancy was otherwise normal. The birth was normal, at term, and the birth weight was 8 lb 2 oz (3685 g). Intubation and intermittent ventilation were required for 1½ minutes after birth,

Fig. 2 Electoretinogram (ERG) recorded from an electrode placed on the bridge of the nose and visual evoked potential (VEP) recorded from the mid occipital region (flash stimulated to both eyes simultaneously while open). Top traces (M.S.) normal. Responses from 2-year-old child for comparison. Case 3, case 2, and case 1 show no clear retinal response, but a cortical response is present, though the usual earlier components are rather small, especially in case 1, but are in keeping with some preservation of function of the central visual pathways to the brain.

and intensive care and nasogastric feeding were required for the first 10 days. Neonatal jaundice was treated with phototherapy.

The mother, a trained nurse, suspected that he had poor vision at 6-8 weeks; nystagmus was noted at 12 weeks, and photophobia was present for the first 4 months. At 12 weeks he was admitted to the local children's hospital for investigations. He was found to have poor vision, optic atrophy, and developmental delay. A raised cytomegalovirus (CMV) titre was found and thought to be the factor responsible for his condition.

He was first seen at the Hospital for Sick Children at 22 months. His parents had noticed some improvement in his vision over the preceding 12 months. On examination he could reach out for objects in all parts of his visual fields; there was bilateral 'pendular nystagmus' with full random eye movements. Pursuit movements were mildly impaired, but there was a gross defect in saccadic eye movements. Pupil reactions were normal, and fundus examination showed slightly pale discs, rather featureless maculae, and mild peripheral retinal pigment epithelial disturbance; the fluorescein angiogram was normal (Fig. 1). There was no recordable ERG, and the visual evoked response (VER), though present, was of low amplitude, and no early components were detectable (Fig. 2).

General examination revealed that he was on the 50th percentile for height and weight and the 75th percentile for head circumference. There was generalised hypotonia, but no other abnormal physical signs. Psychological assessment showed him to be functioning at the 16-month level on a scale for partially sighted children (Reynell-Zinkin scale). The following investigations were normal: full blood

count, ESR, urea and electrolytes, liver function tests, plasma amino acids, toxoplasma, herpes and rubella titres, serum thyroxine, pyruvate and lactate, creatinine phosphokinase and immunoglobulins, urinary aminoacids, urinary reducing substances, midstream urine, nitroprusside test. There were no metachromatic granules on urine examination and no vacuolated lymphocytes in the peripheral blood. Skull x-ray, chest x-ray, and intravenous pyelogram were normal. An electromyogram and nerve conduction studies were also normal. The CMV titres were 1 in 64. CT scan (Fig. 3) showed a large fourth ventricle and prominent cisterna magna, and an appearance consistent with hypoplasia of the cerebellar vermis.

When examined at the age of 4 years he appeared to have good visual acuity, and there was a horizontal and vertical saccade palsy, with head thrusts similar to those seen in ocular motor apraxia used on refixation. The ERG was again absent. He was last seen in 1982, at the age of 8 years, when the visual acuity was 6/18 in each eye with hypermetropic correction. There was 'pendular' nystagmus without fast phases and an alternating divergent squint with left hypertropia. Colour vision was normal. The visual fields were reduced to 30° in each eye. Both discs were pale with attenuated vessels, and there was a mild peripheral retinal pigment epithelial disturbance but no pigment clumping. The ocular movements were again abnormal. There was difficulty in carrying out smooth pursuits, and there was an almost total saccadic defect. There appeared to be great difficulty in initiating eye movements, and eyelid closure and head thrusts were present on attempted refixation. Optokinetic nystagmus was absent, but doll's head movements were full. General assessment revealed muscle hypotonia, severe speech dyspraxia, generalised dis-

Figs. 3a,b The CT scans of case 1 at 22 months showed hypoplasia of the cerebellar vermis.

Fig. 3a

Fig. 3b

Fig. 4a

Fig. 4b

Figs. 4a,b The right optic disc and macula of case 2 at 8½ months. Apart from a mild appearance of optic disc swelling the fundi were normal.

turbance of motor control, disequilibrium, and low normal intelligence.

CASE 2

This male child, the younger sib of case 1, was born after a normal pregnancy and delivered at term. On the second day he developed respiratory stridor and bursts of rapid respiration, especially when handled, but this soon settled. The neonatal period was otherwise uneventful. His mother noticed nystagmus and poor vision soon after birth, and for the first six months he showed little visual attention. He was first seen at the Hospital for Sick Children at 8½ months. There was 'pendular' nystagmus, but he would follow a light, and pupil reactions were normal. Retinoscopy revealed 9 dioptres of hypermetropia in each eye. Fundus examination was normal (Fig. 4), apart from an appearance of mild disc swelling. Fluorescein angiography showed an area of poor choroidal filling below and temporal to the optic disc, but was otherwise normal (Fig. 5). An ERG was of very low amplitude (2 μ V), and the visual evoked response was normal (Fig. 6). General examination revealed generalised hypotonia and developmental delay. Similar investigations to those performed in his sibs were all normal apart from the CT scan (Fig. 6) which showed a similar appearance to his sib.

When reassessed at the age of 2 years he was found to have an ocular motor abnormality similar to his

brother's with a marked abnormality of saccadic eye movements. There were no large head thrusts, but head movements were used in refixation in the absence of normal saccades. The ERG was repeated, and there was a very low amplitude response of 1 or 2

Fig. 5 The fluorescein angiogram showed a transient choroidal filling defect in the right eye but was within normal limits.

Figs. 6a,b The CT scan of case 2 showed cerebellar hypoplasia.

Fig. 6a

Fig. 6b

μ V. He was last seen at the age of 5 years, when his corrected vision was 6/18 right and 6/36 left. There was an alternating divergent squint, but no nystagmus in the primary position. Pursuit movements were normal, but there was a marked abnormality of horizontal and vertical saccadic movements. There was difficulty in initiating saccades, and attempts at refixation were accompanied by head movements in advance of eye movements (Fig. 7). The normal fast component of optokinetic nystagmus was not elicited. Doll's head movements were full. Visual fields were

reduced to about 45°. Fundus examination revealed normal discs and vessels but a mild peripheral retinal pigment epithelial disturbance and an unusual white deposit around both maculae (Fig. 8). General assessment revealed low normal intelligence, a dyspractic speech abnormality, and disequilibrium and motor abnormalities similar to those of his sib.

CASE 3

This male child was born after a normal pregnancy to unrelated parents by a normal delivery, and weighed

Fig. 7a Case 2, showing him about to look to the right from the left.

Fig. 7b He has already thrust his head far to the right and is returning it to the left whilst the eyes achieve their new position.

Fig. 8a

Fig. 8b

Figs. 8a,b The maculae of case 2 at 2 years old showed a white deposit around the fovea in the neural retina.

6 lb 13 oz (3090 g) at birth. He had a brief cyanotic attack soon after birth, but the neonatal period was otherwise normal. There was no relevant family history. At 6 months the health visitor noticed nystagmus and poor visual attention. At 2 months he was noticed to shake his head from side to side; he was also showing signs of poor motor development.

At 4 months he was admitted for investigation of poor vision and developmental delay. He was found to have 'roving eye movements' with poor fixation. Pupil reactions to light were sluggish, and spinning produced only a tonic deviation of the eyes. Fundus examination and a fluorescein angiogram were normal (Fig. 9). The ERG was absent, and the VER was of reduced amplitude (Fig. 2). General examination revealed hypotonia and delayed motor development.

The following investigations were all normal: full blood count, ESR, urea and electrolytes, serum creatinine, liver function tests, plasma amino acids, plasma proteins, immunoglobulins, serum magnesium, phosphate and alkaline phosphatase, creatinine phosphokinase, toxoplasma, rubella, cytomegalovirus, and herpes (TORCH) screen, VDRL, skull x-ray, and chest x-ray. The serum pyruvate and lactate were minimally raised but thought to be of no significance. There were no metachromatic granules on urine examination and no vacuolated lymphocytes in the peripheral blood. CT scan was normal. A provisional diagnosis of Leber's amaurosis was made.

When he was examined again at the age of 3 years his vision was found to be better than anticipated. He would reach out for small objects, even when one or

other eye was covered. Nystagmus was still present, but on this occasion he was found to have an oculomotor abnormality with poor horizontal saccades and obvious horizontal head thrusts similar to those seen in oculomotor apraxia (Fig. 10). Vertical movements were normal. Spinning resulted in only a tonic deviation of the eyes. Fundus examination and fluorescein angiogram were normal. An ERG carried out with skin electrodes with the child awake showed an absent response, but a second ERG carried out under general anaesthetic using a gold foil electrode in the lower fornix revealed a low amplitude response (30 μ V—normal 150 μ V). General examination revealed hypotonia, generalised motor delay, and poor intellectual performance.

He was last seen at the age of 5½ years. Because of mental retardation it was not possible to test his visual acuity formally, but he could reach out for small objects in all parts of the visual field of each eye. To confrontation his visual fields were full, and he was able to match coloured objects accurately. There was no nystagmus or squint, but both pupils reacted very sluggishly to light. There was difficulty in performing horizontal pursuit movements and a marked abnormality of horizontal saccades. Vertical movements were reasonably full. Obvious head thrusts were present on attempted refixation. No optokinetic nystagmus could be elicited. Fundus examination showed mild peripheral retinal pigment epithelial disturbance but was otherwise normal. He still has very poor motor development; he is able to support his weight but unable to walk; he has developed no speech, but has normal hearing, and is severely intellectually subnormal.

Fig. 9a

Fig. 9b

Fig. 9c

Fig. 9a The macula of case 3 at 4 months was normal.
b,c: The fluorescein angiogram was normal.

Discussion

These three patients are of interest firstly because they are part of a subgroup of patients with CRB who retain useful vision, and secondly because they show an association of retinal dystrophy with an oculomotor disorder which is also thought to be congenital in

origin. Most reports have emphasised the poor visual prognosis in CRB, but some studies have reported patients with relatively good visual acuity, when they are old enough to be formally tested.^{12,13} In Alström and Olson's study¹ 79% of cases had visual acuity of hand movements or worse and only 5% had visual acuity of 0.1 (6/60) or better. There appeared to be a decline in vision in later life, which was not related to the development of lens opacities. In the study of Vaizey *et al.*⁸ 6 of 27 children with CRB retained reasonable vision, and 5 could be formally tested. Three had vision between 6/36 and 6/60 and 2 had vision of 6/12 or better. Stanley *et al.*¹³ were able to assess visual acuity in 16 patients in their study and 4 had an acuity of 20/200 or better. Although most children with CRB have poor vision, a minority will develop reasonably good central vision despite having an extinguished or subnormal ERG. This indicates that CRB is a heterogeneous condition or, perhaps more likely, that it is a group of disorders. All three of our patients fall within this group, and they are not the same patients reported by Vaizey *et al.* from this hospital.⁸

In 1952 Cogan²⁴ described a congenital ocular motor abnormality (COA) which he termed ocular motor apraxia, which is characterised by impairment of horizontal gaze with preservation of full random eye movements. Conspicuous head thrusts are present on attempted horizontal gaze. Vertical gaze is usually normal. Horizontal saccades are absent or abnormal, and the fast phase of optokinetic nystagmus is absent horizontally. In children with large

Fig. 10 Case 3. Left: he is about to make a refixation to the left. Right: he has thrust his head far to the left and is making a correcting thrust to the right to get the eye position on target.

obvious head thrusts the diagnosis is not difficult, but in other cases the abnormality of head and eye movements may be more subtle and very variable. In infancy the saccade disorder may easily be missed and the child suspected of having very poor vision because of the absence of visually elicited eye movements. The condition is commoner in boys, but it also occurs in girls.^{25–31} It has been reported in sibs,^{26 29–32} identical twins,³³ and in two successive generations.²⁷ It is thought to be inherited both as a sex-linked and autosomal recessive condition, though some cases are sporadic.³²

Initially the condition was thought to be benign and to improve with age, as it has only occasionally been seen in adults. Some reports have indicated an association of COA with neurological and other systemic disorders; these have been reviewed by Rendle Short³² and Cogan *et al.*³⁴ Neurological abnormalities have included mild hemiplegic ataxia, mental retardation, and delayed motor development. Several patients have shown structural abnormalities of the CNS on neuroradiological investigation. Agenesis of the corpus callosum,^{30 35} hamartoma of the foramen of Monro,³⁵ and cerebellar hypoplasia³⁶ have all been reported. Other patients, however, have had normal air encephalograms and CT scans.^{32 34 37} There have also been two reports of COA in patients with brain stem compression by tumour.^{38 39} Other systemic abnormalities such as web toes, cleft plate, and orofacial digital syndrome have also been reported in the condition.³⁴ Supranuclear palsies of horizontal gaze with compensatory head movements similar to COA have also been reported in ataxia telangiectasia^{40 41} and Wilson's disease,⁴² Huntington's chorea,⁴³ Gaucher's disease,³⁴ and various conditions involving the

cerebellum. An ocular motor defect similar to COA has been seen in spinocerebellar degeneration^{29 34 44 45} and in a closely related condition olivopontocerebellar degeneration.⁴⁶ It has also been reported in association with another cerebellar disorder, Pelizaeus-Merzbacher disease.³⁴ These conditions can be differentiated from COA by the age of onset and other associated clinical features.

In our three cases it is unlikely that the oculomotor defect is due to a constricted visual field giving rise to poor visual fixation, because even reflex saccades were abnormal.

It is interesting that both COA and CRB have been reported in association with hypoplasia of the cerebellar vermis, and in addition cerebellar disease and tapetoretinal degeneration coexist in several conditions affecting children. Carpenter *et al.*⁴⁷ reported three sibs under the age of 2 years with olivopontocerebellar atrophy, who had fundus appearances consistent with a tapetoretinal degeneration, though no ERG was performed no pathological findings on the eye were available. De Jong *et al.*⁴⁸ reported three children under the age of 4 years with OPCA, who had a retinal dystrophy confirmed by the presence of an extinguished ERG. Pathological examination of the eyes of one child who died at 11 months showed absence of rods and cones in the posterior retina. Ryan *et al.*⁴⁹ found abnormal retinal pigment epithelium and photoreceptors at post-mortem examination of the eyes of two children with histologically proved OPCA. The association of OPCA and an apparently acquired tapetoretinal degeneration has also been reported in adults.⁵⁰ Spinocerebellar degeneration has also been described in association with an apparently acquired form of tapetoretinal degeneration, which first appears in adult life, affect-

ing the macula initially and later involving the peripheral retina.^{51,52} A retinal dystrophy indistinguishable from Leber's amaurosis has been reported in association with Joubert's syndrome; a recessively inherited condition comprising episodic hyperpnoea, abnormal eye movements, ataxia, psychomotor retardation, and hypoplasia of the cerebellar vermis.^{53,54} Tapetoretinal degeneration and oculomotor abnormalities have also been described in association with mitochondrial cytopathy, a multisystem disorder of children and adults,⁵⁵ but the usual oculomotor disorder is 'ophthalmoplegia plus'⁵⁶ and is a peripheral muscular disorder affecting all modalities of eye movements.

Cogan *et al.*³⁴ have reported two sibs who were found to have COA and normal fundi in infancy, who when re-examined seven years later were found to have a typical pigmentary retinopathy with an extinguished ERG. Our three cases in which diagnosis of a retinal dystrophy was made before a saccade palsy was evident confirms the association of supranuclear gaze disturbance and tapetoretinal degeneration in children. Although only one of our cases had typical ocular motor apraxia, it appears that these five cases represent a new subgroup of those disorders which have in common abnormalities of brain stem and cerebellum, supranuclear gaze disturbance, and tapetoretinal degeneration. Klein has pointed out that there may be a specific group of disorders with cerebellar and retinal involvement,⁵⁷ and Nickel and Hoyt have emphasised that the cerebellar vermis begins to appear as a distinct structure at the same stage of embryogenesis (12 weeks) that active differentiation of the photoreceptor layer of the retina is taking place.¹² Both CRB and COA have individually been reported in association with hypoplasia of the cerebellar vermis, and in the first two cases reported here the CT scan appearances were consistent with cerebellar hypoplasia.

These three cases raise a further question about the nature of the condition of Leber's amaurosis. Most cases are thought to be autosomal recessive in inheritance, yet there is a wide variation in the severity of the visual loss and also in the associated systemic features. Are the cases reported here a genetic subtype, as may be those cases with renal or neurological disorders, or are they all part of a wide spectrum of disease in a single genetically determined disorder? It is interesting in this respect that Waardenberg *et al.*⁵⁸ reported two patients blind from birth with presumed CRB, who married and had two normal children, suggesting that there are at least two different recessive genes causing this disorder. The answers to these questions are of more than academic interest, as they are important in allowing an accurate visual and educational prognosis to be made and in predict-

ing which patients need further investigation to rule out systemic associations.

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