Tapetoretinal degeneration in the cerebro-hepato-renal (Zellweger's) syndrome

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SUMMARY Electrophysiological and histopathological study of a baby suffering from Zellweger's syndrome and presenting progressive retinal dysfunction showed this to be related to degenerative changes in the photoreceptor cells and pigment epithelium and to defective myelination of the optic nerve. Disturbances of bile acid and lysine metabolism were also demonstrated, lending support to the concept that Zellweger's syndrome is attributable to a widespread inadequacy of intracellular oxidative function.

The multisystem congenital disorder designated as the cerebro-hepato-renal syndrome¹ was first defined as an entity by Zellweger and colleagues in 1964.² Severe dysfunction of the central nervous system is associated with progressive muscular hypotonia and, not infrequently, seizures. Defective liver function is manifested as jaundice and hepatomegaly with, in some cases, hypoprothrombinaemia and gastrointestinal haemorrhage.³ Clinical evidence of renal involvement in the form of proteinuria is generally minor, though multiple cortical cysts are a characteristic finding at necropsy.³⁻⁵ A number of other organs, including the thymus and pancreas, the latter manifested as islet cell hyperplasia and hypoglycaemia,⁶ may be abnormal, and calcific stippling of the bony epiphyses is common.^{7,8} Babies affected by the cerebro-hepato-renal syndrome have a characteristic appearance caused by a high forehead and 'pear shaped' skull, flat supraorbital ridges, micrognathia, high arched palate, and redundancy of the skin of the neck.³ Malformation of the ears,³ camptodactyly,³ and other limb deformities are also well documented. Death within the first few months of life is almost invariable because of progressive cerebral dysfunction, feeding difficulties, and, less often, gastrointestinal haemorrhage.³

Ocular disturbance in the cerebro-hepato-renal syndrome is also frequent and can take a variety of forms. The globes may appear unduly prominent as part of the overall facial abnormality, enhanced by

puffiness of the eyelids,³ and nystagmus is a reflection of brain dysfunction. Defects of the globe per se can involve both anterior and posterior segments, presenting variously as corneal clouding, cataract, glaucoma, optic nerve hypoplasia and tapetoretinal dystrophy^{1,3,4,9-15} (D. Toussaint, personal communication). However, descriptions of the ocular histopathology are relatively few, and in this report we document the findings in a baby presenting evidence of tapetoretinal dysfunction.

Case history

A female Pakistani baby was born on 2 September 1979, the product of a consanguineous marriage. Birth weight was 2340 g following a normal pregnancy and delivery. On the first day an abnormal facial appearance was observed (Fig. 1) due to a high forehead, epicanthus, and flat supraorbital ridges and bridge of the nose, these latter making the eyes appear to be prominent. Other features included gross hypotonia, jaundice, hepatomegaly, and palpable lobulated kidneys.

The eyes were first examined at 3 weeks of age. Although there was a reaction to light, no following or optokinetic responses could be elicited. Ocular movements were full, with jerk nystagmus on lateral gaze. The eyes were of normal size, with no discernible abnormality of the anterior segments. Pupillary reactions, intraocular pressures, and optic discs were normal, but the retinal arteries were attenuated. A red lesion approximately one-third of the disc diameter in size was seen at the right macula (Fig. 2),

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Fig. 1 Dysmorphic facies with high forehead and prominent eyes due to flat supraorbital ridges.

while the left macular region contained a central area of deep pigment clumping surrounded by a rim of depigmentation (Fig. 3).

Two siblings, both male, had been born previously. The first born in 1973 is alive and well, but the second born in 1978 died 5 hours postnatally. Post-mortem examination revealed renal cysts. There have been no miscarriages and there is no further relevant family history.

INVESTIGATIONS

Liver function tests were consistently abnormal, including serum bilirubin $140 \mu\text{mol/l}$, lactic dehydrogenase 1346 IU/l , serum glutamic-oxaloacetate transferase 546 IU/l , and serum glutamic-pyruvate transferase 187 IU/l . Haemoglobin was 20.6 g/dl , white cells $11.7 \times 10^9/\text{l}$, and platelets $150 \times 10^9/\text{l}$. Prothrombin time was normal at 12 s (control 12 s). Urine analysis for bile acids showed the presence of

Fig. 2 Macular region of the right fundus presenting a focal zone of red pigmentation.

dihydroxycoprostanic and trihydroxycoprostanic acids (46% of 5% respectively of the total) and reduced amounts of their related chenodeoxycholic and cholic acid derivatives (7% and 18% respectively). Liver biopsy showed enlargement of the portal tracts by infiltration with macrophages. Periportal hepatocytes and portal macrophages contained sparse

Fig. 3 Macular region of the left fundus with central area of clumped pigment with a surrounding faint halo of depigmentation.

Fig. 4 Electron micrograph of liver biopsy showing punctate intracytoplasmic iron deposits. Uranyl acetate/lead citrate ($\times 6500$).

pigment granules. Excess iron was observed in hepatocytes and in portal macrophages (Fig. 4).

A pipecolic acid loading test was performed. The 331 ml 24-hour pretest urine specimen contained 24.3 mg pipecolic acid, a substance not normally detectable in urine. Following a 400 mg oral pipecolic acid load the urinary pipecolic acid output increased but the α -amino adipic acid did not, indicating a metabolic block between pipecolic acid and α -amino adipic acid.

Ultrasound indicated large cystic kidneys and the intravenous pyelography showed hydronephrosis.

With a noncorneal electrode no electroretinogram (ERG) could be elicited on 3 occasions, whereas with a gold-foil electrode, in contact with the globe, a low-amplitude response was obtained, b wave (a-b peak to peak) 11 μ V right and 9 μ V left. This ERG was recorded only at 1 month of age, there being no detectable response at 2 months. The wave form of a visual evoked response (VER) to a flash stimulus at 1 month was simple, as compared with that normally seen at this age (Fig. 5). No consistent VER could be elicited one month later. ERG and VER measurements were made with a Medelec MS6 modular electrophysiological system fitted with a DAV6 digital averager.

Over the ensuing 10 weeks the ocular findings, in particular the red lesion at the right macula, remained unchanged. The baby failed to thrive, feeding difficulties and jaundice persisted, and death from bronchopneumonia occurred at 13 weeks of age.

NECROPSY FINDINGS

Macroscopic abnormalities were seen in the liver, kidneys, and brain. The liver weighed 170 g and had a yellow-green appearance, with histological findings comparable to those previously described in the biopsy specimen. Both kidneys were enlarged (combined weight 100 g) and had multiple cortical cysts (Fig. 6), which represented mainly markedly dilated maldeveloped cortical tubules, as a component of a focally dysplastic renal cortex. The surface of the brain contained abnormally small and broad gyri (pachymicrogyria) (Fig. 7). The white matter in the centre of the brain appeared unusually pink. Histological sections of the brain showed, inter alia, islands of neurones remaining between the ependyma and cortex, particularly in the temporal lobes; similar changes of incomplete neuronal migration were present in the external granular layer of the cerebellum. Myelination was less developed for the age than normal, and in frozen sections of brain stained

Fig. 5 Flash VER compared with results obtained from a normal infant (lower traces). Those from the case reported here (denoted by Case in the figure) at $3\frac{1}{2}$ weeks show a recognisable waveform which is not present at 8 weeks, indicating not only failure of normal maturation but also deterioration.

with oil red O and Sudan black B the commonest cell in the white matter was the swollen astrocyte. In essence the brain changes were those of delayed neuronal maturation, retarded myelination, and lipid-containing astrocytes.

Ocular pathology. Neither eye showed any external abnormality, but owing to a delay of several hours before fixation in formalin both showed some puckering and folding of the retina around the macula.

Light microscopy. There was no apparent abnormality of the corneoscleral envelope in either eye, and the angles of both anterior chambers were normally formed and patent. The lens and ciliary body in both eyes were normal, and the sole finding of note in the anterior segments was generalised lacy vacuolation of the pigment epithelium of the iris. The retinae had suffered considerable autolysis with artefactual detachment, but even in places where separation had not occurred there was unmistakable loss of photoreceptor outer segments affecting chiefly the rods (Fig. 8). Atrophic flattening of the retinal pigment epithelium was widespread, with focal deficiencies and migration of occasional cells away from their attachment to Bruch's membrane (Fig. 9). Small amounts of necrotic debris were also present

Fig. 6 Multiple cortical cysts in the bisected kidneys.

Fig. 7 The surface of the brain is characterised by both unusually small and large gyri to create a 'cobblestone' appearance. ($\times 0.125$.)

between the degenerate epithelium and photoreceptor cells. The inner layers of the retinae were not noticeably abnormal and showed a conventional organisation. Both optic discs showed an overlying Bergmeister's papilla, while the optic nerve were sites of extensive demyelination and some gliosis.

Electron microscopy. A piece of retina and choroid from the perimacular zone of the right eye was post-fixed in buffered glutaraldehyde for transmission electron microscopy. Many of the photoreceptor cells were completely degenerate and were represented by

sparse debris, some of it in the form of multilaminated myelin figures (Fig. 10). Others had shed most, if not all, of their outer segment discs, and the inner segments showed considerable loss of mitochondria with exposure of the ciliary roots. Residual mitochondria in these degenerate cells were frequently swollen with ring and other abnormal cristae. No abnormality was recognised in other layers of the neuroretina. The pigment epithelium was flattened and some cells contained somewhat less melanin than normal. A general loss of microvillous processes on the inner surface of the epithelium was observed. Some pigment-containing cells were lying free in the subretinal zone and exceptionally included unusually angulated bodies of moderate electron density presumed to be premelanosomes (Fig. 11).

Fig. 8 The retina close to the optic disc shows an essentially normal organisation, but there is almost total loss of the photoreceptor outer segments and migration of an atrophic pigment epithelium. (Haematoxylin and eosin, $\times 114$.)

Fig. 9 The retinal pigment epithelium is flattened and some melanin-containing cells are intermingled with necrotic photoreceptor cell debris in the subretinal space. (Haematoxylin and eosin, $\times 114$.)

Fig. 10 *Electron microscopy of the degenerate photoreceptor outer limbs reveals multilaminated residues and unusual prominence of the ciliary roots (arrow) due to relative sparsity of mitochondria. (Uranyl acetate/lead citrate, $\times 6685$.)*

Fig. 11 The retinal pigment epithelium is flattened with absence of villous processes and incipient detachment from Bruch's membrane. A detached cell on the inner surface of the epithelial monolayer contains several curious angular bodies presumed to be defective and minimally pigmented melanosomes. (Electron micrograph, uranyl acetate/lead citrate, $\times 6662$.)

Discussion

The combined clinical and pathological findings in our case adequately substantiate the diagnosis of Zellweger's or cerebro-hepato-renal syndrome as defined in the reports establishing the nosological identity of the condition.¹⁻³

The most extensively studied changes concern the brain which, to external examination, presents either an excessive number of small gyral infoldings (polymicrogyria)^{5 16 17} or a combination of small densely packed and unusually broad gyri (pachymicrogyria).^{3 9 10} Histological examination shows changes suggestive of arrested maturation manifested as incomplete migration of cortical neurones and defective myelination of nerve fibres in the white matter with secondary gliosis, which may be associated with the accumulation of sudanophilic material in the phagocytic elements of the central nervous system.¹⁰ The latter have been termed globoid cells, and electron microscopy suggests that they contain multilaminated cytoplasmic bodies.^{9 16} Whether the deficiency of myelin and consequent reduction in volume of the white matter is a primary fault in synthesis¹⁷ or, as is perhaps more likely, a destructive process^{9 10 16} is unresolved. The dysplasia affects the cerebellum and brain stem structures such as the medullary olives^{9 10 16} in addition to the cerebrum.

The hepatic disturbance can assume a variety of forms but according to most reports presents as mild enlargement related to diffuse parenchymal cell damage and intralobular fibrosis.⁸ Cholestasis and portal fibrosis characterise some infants¹⁸ and, as in the present case, iron deposition may be found.^{3 4 6 8} The origin of the liver disorder is obscure but is possibly secondary to metabolic abnormalities^{5 18} rather than to a primary maldevelopment.

Multiple cysts in the renal cortices are an integral part of the syndrome, some representing dilated Bowman's spaces around glomerular remnants^{3 8 9 19} with surrounding fibrosis^{4 5} and others, as here, being the result of tubular dilatation^{5 8} caused by focal dysplasia of the cortex.

Although the character of the involvement may vary, ocular involvement in the cerebro-hepato-renal syndrome is common. Nystagmus features in most cases and is likely to be neurological rather than ocular in origin, particularly as in our case it was observed at only 3 weeks of age and then only on lateral gaze.

Abnormalities of the anterior segment include corneal clouding^{3 4 9 11 12 14} which may be associated with raised intraocular tension^{11 12} or iridocorneal adhesion and deficiency in the endothelial lining of Descemet's membrane.¹⁴ Bilateral congenital cataracts are not uncommon,^{1 3 4 9 14 15 18 20} and, while

it does not explain their occurrence, their presence in Zellweger's syndrome with its attendant articular cartilage calcification invites comparison with chondrodystrophia calcificans congenita (Conradi's syndrome), in which lens opacities are usual.²¹ Alternatively the concomitance of renal tubular dysfunction, brain abnormalities, and cataracts in both Zellweger's syndrome and Lowe's (oculocerebrorenal) syndrome²² may be significant. A recent report¹⁵ suggests that heterozygotes also may develop comparable lens opacities. A single report of Brushfield's spots in the iris³ may be purely coincidental, as may the finding of persistent Bergmeister's papillae in the present case. The pathogenesis of the glaucoma complicating some cases¹⁰⁻¹² is unknown. The vacuolation of the iris pigment we describe has not been commented on in other reports, and, though characteristic of the eye in diabetes mellitus and Hurler-Hunter forms of mucopolysaccharidosis, it can from personal experience sometimes present as a nonspecific finding in many states linked with metabolic dysfunction.

With the knowledge of ocular and visual pathway histopathological findings it is interesting to consider the possible significance of the electrophysiological investigations made at various times during life. The ERG (gold-foil electrode) at one month of age with a b wave amplitude of the order of 10 μ V was grossly reduced even allowing for age²³ and below the sensitivity of the noncorneal electrode, thus explaining our failure to demonstrate an ERG using this method. The absence of an ERG one month later could have been due to progression of the pathological process, and it is significant that the ERGs were absent in each of 4 cases examined by Hittner and her colleagues¹⁵ after a minimum of 2 months' survival. The VER at 1 month of age was present but abnormal, and although a large negative wave was always seen at 300 ms the preceding positive wave (200 ms), a prominent component of the normal response, was of reduced amplitude. One month later no consistent VER could be demonstrated clearly confirming that in Zellweger's syndrome degenerative features are superimposed upon a distinct malformation.

The macular regions of the 2 eyes of our case exhibited different features. It would be interesting to know whether the pigmentary disturbance we observed at the left macula was the same as the retinal hole without detachment in the second case reported by Opitz *et al.*³ The slightly raised red lesion at the right macula was assumed to be a haemorrhage, but, unlike a haemorrhage, no change in its shape or colour occurred over 10 weeks of observation. It should also be noted that in our case there was no bleeding diathesis. Unfortunately due to retinal distortion the macular regions could not be identified histologically.

Posterior segment abnormalities of the kind seen in the present case may be an extension of the anomalous central nervous system development. The first report of sensory disturbance was that of Punnett and Kirkpatrick,¹¹ the child they documented being unable to follow light at the age of 4 months and presenting a fundus appearance characterised by hypoplasia of the optic disc and pigmentary disturbance. Subsequent authors described attenuation of the retinal vasculature^{10,13} and absence of electroretinogram response.^{9,13} The first histological description of retinal pathology appears to have been that by Volpe and Adams,¹⁰ wherein they referred to abnormal clumps of pigment epithelium in the peripheral retina associated with reduced numbers of photoreceptor and ganglion cells. Haddad and colleagues¹⁴ described atrophy and gliosis of the optic nerve and retinal nerve fibre layer as well as degeneration of the photoreceptor cells in the macular area. The findings in our own case confirm the outer retinal and optic nerve abnormalities. In retrospect it is surprising that the pupillary reactions were preserved and that there was no dilatation such as is commonly seen in bilateral optic nerve disease. The sequence of events at the tapetoretinal level is obscure, but the relative sparing of the pigment epithelium in a four day old neonate¹⁴ suggests that the primary defect is in the neuroretina. Toussaint (personal communication) undertook a detailed examination of the ocular tissues in an affected baby dying at the age of 7 weeks, and here also the degenerative changes in the photoreceptor outer segments appeared to outweigh the disturbance of the pigment epithelium. The absence of myelin in the optic nerve at the age of 3 months, as pertained in the present case, is abnormal and was probably a reflection of the defective myelination which characterises the brain abnormality in Zellweger's syndrome.

The fundamental fault in the cerebro-hepato-renal syndrome is unknown, but there is increasing evidence of a recessively inherited autosomal gene defect.^{3-5,8} It has been suggested that the same defective gene could, by acting at sequential stages in development, be responsible for both the developmental abnormalities and the metabolic disturbances seen in the syndrome.^{9,16}

The first metabolic derangement to be described was excessive iron binding by the tissues as demonstrated by electron microscopy in the liver of the present case.^{3,24} But this is not a constant finding, and more recently the deposition of iron has been attributed simply to impaired utilisation in association with a failure to thrive and depressed erythropoietic activity.^{6,8} So far as the eye is concerned iron has been demonstrated in the epithelium of the cornea and ciliary body (nonpigmented) by Volpe and Adams,¹⁰

but others,¹⁴ including ourselves, have obtained negative results.

Accumulation of pipecolic acid in Zellweger's syndrome, such as was demonstrated in the present case, was first described by Danks and others⁸ and since confirmed by Trijbels and colleagues,²⁵ although a similar disorder presenting a little later in infancy associated with hyperpipecolataemia had already been documented.²⁶ Pipecolic acid originates from the breakdown of lysine through a subsidiary metabolic pathway and is normally present in the blood in trace amounts only: its role in the symptomatology of Zellweger's syndrome is obscure, although an amine derivative, piperidine, can produce brain damage in mice,²⁷ and studies in rats indicate that the pipecolic acid pathway is the principal mode of lysine catabolism in the nervous system.²⁸

Defective oxidation of bile acid precursors to cholic and chenodeoxycholic acids such that intermediary products are detectable in the serum and urine has also been described.^{18,29} The finding of dihydroxy- and trihydroxy-coprostanic acids in the urine of the present case, the former accounting for almost half the urinary bile acid excretion, is in keeping with these reports. It is possible that these and other bile acid precursors are toxic to liver cells and account for the cellular damage in this organ.¹⁸

To explain the widespread metabolic disturbances in Zellweger's syndrome it has been proposed that there is a generalised disorder of oxidative function caused by defective mitochondrial and peroxisomal activity, Goldfischer and colleagues³⁰ having earlier described structural and functional anomalies in these organelles. Abnormal morphology of mitochondrial cristae was seen in the retinal photoreceptors in the present case, but it remains to be seen whether such alterations are more than a nonspecific degenerative product.

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