Warburg (HARD±E) syndrome without retinal dysplasia: case report and review

M F D ATTIA,¹ J BURN,² J H McCARTHY,³ D P PUROHIT,⁴
AND D W A MILLIGAN⁵

From the Departments of ¹Ophthalmology, ⁴Neuropathology, and ⁵Child Health, Newcastle General Hospital, Newcastle-upon-Tyne; the ²Department of Human Genetics, University of Newcastle-upon-Tyne; and the ³Department of Pathology, South Shields General Hospital.

SUMMARY Warburg syndrome is a recently defined autosomal recessive oculocerebral syndrome. It was previously given the acronym HARD±E, indicating what were regarded as the pathognomonic features, namely hydrocephalus, agyria, and retinal dysplasia with or without encephalocele. We report the case of a male infant with the typical cerebral features of hydrocephalus, agyria, and pseudoencephalocele, but without retinal dysplasia. Peters' anomaly and optic nerve hypoplasia were the main ocular defects. We believe that anterior chamber defects and optic nerve hypoplasia are the ocular defects more directly related developmentally to the cerebral defects. Definition of ocular defects is important, since diagnosis and counselling rely heavily on ocular signs, which help to distinguish this syndrome from neural tube defects in general.

Congenital cerebral abnormalities were reported to be associated with a variety of eye defects. In the absence of polydactyly and polycystic kidneys, which characterise the Meckel syndrome,¹ the association of hydrocephalus, agyria, and in some cases encephalocele with retinal dysplasia was recognised as a specific syndrome and was given the mnemonic HARD±E syndrome by Pagon *et al.*² More recent reports and reviews³⁻⁵ have emphasised the variability of expression of this autosomal recessive disorder. Pagon *et al.*³ suggested that the eponym Warburg syndrome be used instead of HARD±E.

We report a case with typical cerebral features of Warburg syndrome but without retinal dysplasia.

Case report

A full-term white male baby was born to young Caucasian unrelated parents. The pregnancy was normal, with no history of maternal disease or drug intake. Previous obstetric history included a spontaneous abortion at 10-12 weeks and the birth of a normal female infant. No family history of any congenital abnormality could be elicited. Birth weight was 2960 g, length 48 cm, and head circumfer-

ence 33.7 cm. External examination (Figs. 1, 2) showed micrognathia, hypertelorism, low-set ears, and a cleft palate extending to the gingival margin. The occipital region showed a reducible, non-pulsatile protrusion, overlying a small bony defect. The overlying skin showed a tuft of hair, covering a dermal sinus. A head scan revealed grossly dilated lateral and third ventricles and absent corpus callosum. A body scan showed the right kidney to be enlarged, with large cystic spaces. Both eyes were enlarged and protuberant, with increased corneal diameter to 13 mm each. There were localised central corneal opacities, denser in the left than in the right cornea (Fig. 1). The pupils were small and fixed, with a transverse diameter of 2.9 mm (right) and 1.7 mm (left). The irides appeared stretched and slightly atrophic. The intraocular pressure was raised to 26 mmHg (right) and 28 mmHg (left), as measured with a Perkins applanation tonometer. A faint red reflex was evident in both eyes. There was no obvious nystagmus or strabismus. Chromosomal analysis revealed a normal male karyotype. Serology titres for herpes simplex, rubella, and cytomegalovirus were not increased. The infant died at the age of 4 days.

Post-mortem examination confirmed the facial anomalies. Other abnormalities were confined to the eyes, brain, and urinary system. There was a

Correspondence to Dr M F D Attia, Department of Ophthalmology, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ.

Fig. 1 Front view of the face, showing bilateral central corneal opacities.

marked right hydronephrosis and hydroureter, caused by a stricture of the distal end of the ureter. The left kidney showed multiple nodules of focal renal dysplasia in the upper pole.

OCULAR PATHOLOGY

Shortly after death both eyes were examined under the biomicroscope. The right eye (Fig. 3) showed a

Fig. 2 Lateral view of the head, showing buphthalmos, micrognathia, low-set ear, and pseudoencephalocele.

Fig. 3 The right eye, as seen through the biomicroscope. Note the central corneal stromal opacity, central posterior corneal defect, and very shallow anterior chamber, which is obliterated centrally.

faint central corneal stromal opacity and a posterior central stromal defect, consistent with Peters' anomaly. The anterior chamber was very shallow at the periphery and absent centrally, with apparent adhesions of the iris-lens diaphragm to the posterior surface of the cornea, at the pupillary area. The left eye showed a denser central corneal stromal opacity. Neither corneal stromal defect nor central adhesions between the cornea and iris-lens diaphragm could be detected. The anterior chamber was also very shallow.

Examination of the fixed specimens showed both eyes to be enlarged (diameters right and left: 21 mm transverse, 19 mm anteroposterior, and 20 mm superoinferior). On cross section each eye showed an optic disc, an optic nerve stump, and retinal blood vessel of normal appearance. Both retinæ were attached, with no folds or colobomata. A thin, translucent, non-vascular band extended from the optic disc to the posterior surface of the lens in each eye.

Microscopic examination of the right eye (Fig. 4) confirmed the central corneal defect involving the posterior stroma, with complete absence of the endothelial cell layer and Descemet's membrane over the defect. The pupillary margin of the iris showed evidence of adhesion to the margins of the central corneal defect, with no inflammatory cellular infiltrate detected. The left eye (Fig. 5) showed no central corneal defect apart from a rather thin Descemet's membrane. The iridocorneal angle was

Fig. 4 Cross section of the right eye. Note the posterior central corneal defect, posterior lenticonus, and normal appearance of the retina. (H and E, $\times 3$).

normal and open bilaterally, with a normal trabecular meshwork and canal of Schlemm. The lens capsule was intact in both eyes. There was a right posterior lenticonus and central lenticular calcification (Fig. 4) and a left posterior cortical cataract. Both retinæ showed a normal layering with a normal retinal pigment epithelium. Retinal ganglion cells could be detected in their normal place but were diminished in number. There was no evidence of rosette formation in either retina when multiple sections were studied. Optic discs were confirmed bilaterally by the absence of overlying retinal tissue. The lamina cribrosa showed no evidence of cupping. Both optic nerve stumps were of normal size. They were formed mainly of glial cells and failed to show

Fig. 5 Cross section of the left eye. Note the thick cornea, the thin sclera, and the normal appearance of the retina. (H and E, $\times 2.7$).

the staining reactions either for nerve fibres (axons) or for myelin.

NEUROPATHOLOGICAL FINDINGS

The skull was large. The dura mater was normal, but the falx cerebri was very short. The cerebrum showed total agyria, with the longitudinal and Sylvian fissures only slightly formed. Olfactory bulbs and tracts, optic nerves, chiasma, optic tracts, and lateral geniculate bodies were not identified. Coronal section of the cerebrum (Fig. 6) showed gross hydrocephalus and a continuous ventricular cavity, due to the absence of septum pellucidum and roof of the third ventricle. The basal ganglia, thalamus, and hypothalamic structures were seen only as a bilateral mass of grey matter. In most places the cerebral cortex and white matter were reduced to a thin strip, which on histological examination showed a cortex formed by neurons lacking the orderly, layered arrangement, and a very sparsely myelinated white matter containing islands of migrating neuroblasts. The corpus callosum was severely hypoplastic and visible only as a nodular ridge. In the posterior fossa a Dandy-Walker malformation was identified which had caused distortion of the cerebellar hemispheres and brain stem and widening of the floor of the fourth ventricle. The cerebellar vermis showed hypoplasia and severe cortical dysplasia. The cerebellar hemispheres showed a moderate cortical dysplasia. The cerebellar nuclei and the nuclei of the brain stem were identified, and the cranial nerves emerging from the brain stem and their nuclei were normal.

The aqueduct of Sylvius was also normal. The bulging of the scalp over the small occipital defect was due to a pseudoencephalocele, since there was no histological evidence of its continuity with the cranial cavity or the presence of meningeal or neuroglial tissue.

Discussion

The acronym HARD $\pm$ E was applied to cases showing hydrocephalus, agyria, and retinal dysplasia with or without encephalocele, based on early reports.²⁻⁸ The cases reported by Warburg⁹ were also suspected of being related but were not included owing to insufficient evidence. Pagon *et al.*,³ Bordarier *et al.*,⁴ and Whitley *et al.*⁵ have redefined the syndrome in the light of recent reports. They considered that a less restrictive name than HARD $\pm$ E was necessary. The suggestion of Pagon *et al.*³ to call it Warburg syndrome was accepted in recognition of the pioneer work of this researcher.¹⁰

Retinal dysplasia and non-attachment were found in almost all of the eyes studied histologically. In the present case, however, both retinæ were normally

Fig. 6 Coronal sections of the cerebrum, showing agyria, hydrocephalus with a large single ventricular cavity, and absence of optic nerves and chiasma.

attached. No rosette formation could be detected to indicate retinal dysplasia. Lahav and Albert¹¹ postulated that retinal dysplasia is caused by cellular proliferation of the inner layer of the optic cup, which may be accompanied by folding of the retina. This can occur as an abortive response of a retina, damaged by a number of factors, such as viral infection. They also suggested that orderly retinal development may depend on the organising influence of an adjacent retinal pigment epithelium. Hence non-inflammatory retinal dysplasia usually develops

over areas devoid of pigment epithelium and in congenitally non-attached areas. This indicates that retinal dysplasia is secondary to retinal non-attachment during a faulty development of the optic vesicle. As it is a common, non-specific, and non-pathognomonic abnormality,¹¹ it is not appropriate to consider retinal dysplasia a primary major component of the Warburg syndrome.

The ocular signs of Warburg syndrome have been listed in recent reviews.^{3,5} They included different degrees of Peters' anomaly, unilateral and bilateral.

There were also cases with a combination of central and peripheral anterior chamber defects^{3*} and cases with peripheral defects only.³ In the cases with Peters' anomaly central corneal opacity was the commonest sign. Other opacities in the media were also common, namely, congenital cataract and persistent hyperplastic primary vitreous. A degree of both was found in the case reported here. The posterior lenticonus seen in this case has also been previously reported.¹² When a clear view of the fundus could be achieved, a pale non-attached retina, together with retinal folds, would be the commonest sign expected. Optic disc hypoplasia and colobomata may also be seen. Abnormalities of the size of the globe were frequent, including microphthalmia and, less commonly, buphthalmos, as in the present case.

Bilateral optic nerve hypoplasia was prominent in the case reported here. It is believed to result from a failure of the retinal ganglion cells to form nerve fibres while the mesodermal component of the optic nerve develops, forming an optic disc and retinal blood vessels.¹³⁻¹⁵

Yanoff *et al.*¹³ reported a case with striking similarities to our case, including agyria, hydrocephalus, cerebellar hypoplasia, clouded corneas, micrognathia, low-set ears, and unilateral hydronephrosis. Retinal dysplasia was also not detected. The main ocular feature in that case was bilateral optic nerve aplasia, the pathogenesis of which is believed to be similar to that of optic nerve hypoplasia.¹⁴ The absence of the mesodermal component recognised by the absence of optic discs and retinal blood vessels is probably due to lack of induction caused by the absence of nerve fibres.^{13,14}

In the case reported here the possibility of optic nerve atrophy secondary to glaucoma rather than primary hypoplasia could be excluded, as the intraocular pressure was only slightly raised, and that was mainly compensated for by enlargement of the globes, with no definite cupping of the optic discs.¹⁶

The posterior corneal defect in Peters' anomaly could be explained by an incomplete migration of the initial two waves of mesenchymal cells, which form the corneal endothelium with its Descemet's membrane and then the corneal stroma.^{17,18}

Johnston¹⁹ concluded that the cephalic neural crest provides the origin for most facial and ocular structures apart from the retina and lens, epithelial tissues, vascular endothelia, and skeletal muscle cells. He suggested that the neural crest cells, forming the mesenchyme of the frontonasal processes, are derived from the forebrain neural folds and that the formation of the neural tube and crest may depend on the same inductor. Inadequate induction could result in simultaneous deficiencies of both structures. The frontonasal crest must form a relatively large mass of

cells in a limited time to achieve normal primary palate formation. Experimentally, reducing the number of these crest cells in the chick and mouse embryos resulted in cleft palate with associated brain and eye defects.

Bahn *et al.*²⁰ introduced a classification of corneal endothelial disorders based on neural crest origin. They postulated that Peters' anomaly, together with other anterior chamber cleavage syndrome variants and congenital glaucoma, is caused by an abnormal neural crest cell migration.

The present case shows a combination of cleft palate, Peters' anomaly, and a deficiency of forebrain tissue including the cerebral cortex, diencephalon and sensory retina, which shows a deficiency of retinal ganglion cells causing optic nerve hypoplasia. All these defects could be caused by a developmental failure of the forebrain and its associated neural crest. Optic nerve hypoplasia, together with Peters' anomaly and other anterior chamber defects, could be considered the ocular abnormalities more directly related developmentally to the brain defects in Warburg syndrome.

Three associated anomalies in the case reported here are worthy of comment. Micrognathia was reported in three other cases^{4,13} and unilateral hydronephrosis in one case.¹³ Cleft palate was not reported in the literature but has been noted in another case (P Farndon, unpublished observation).

Warburg syndrome is regarded as being an autosomal recessive trait. This is supported by its frequent occurrence in sibs,^{3,4,7,12,21} the consanguinity of parents in one family,⁷ the good health of all the parents involved, and the lack of evidence of any other aetiology, such as maternal infection or drug intake. The diagnosis of Warburg syndrome is important so that the parents can be advised of its 25% recurrence risk and of the possibility of prenatal diagnosis by detailed ultrasound study. The ocular signs are the major clues to the clinical diagnosis of Warburg syndrome in a neonate with a major neurological deficit and a demonstrable hydrocephalus with or without a posterior encephalocele.

References

- 1 Fried K, Liban E, Lurie M, Friedman S, Reisner SH. Polycystic kidneys associated with malformations of the brain, polydactyly and other birth defects in newborn sibs. *J Med Genet* 1971; **8**: 285-90.
- 2 Pagon RA, Chandler JW, Collie WR *et al.* Hydrocephalus, agyria, retinal dysplasia, encephalocele (HARD±E) syndrome: an autosomal recessive condition. *Birth Defects* 1978; **14**: 233-41.
- 3 Pagon RA, Clarren SK, Milam DF Jr, Hendrickson AE. Autosomal recessive eye and brain anomalies: Warburg syndrome. *J Pediatr* 1983; **102**: 542-6.
- 4 Bordarier C, Aicardi J, Goutieres F. Congenital hydrocephalus

- and eye abnormalities with severe developmental brain defects: Warburg syndrome. *Ann Neurol* 1984; **16**: 60–5.
- 5 Whitley CB, Thompson TR, Mastri AR, Gorlin RJ. Warburg syndrome: lethal neurodysplasia with autosomal recessive inheritance. *J Pediatr* 1983; **102**: 547–51.
- 6 Walker AE. Lissencephaly. *Arch Neurol Psychiatr* 1942; **48**: 13–29.
- 7 Chemke J, Czernobilsky B, Mundel G, Barishak YR. A familial syndrome of central nervous system and ocular malformations. *Clin Genet* 1975; **7**: 1–7.
- 8 Winter RM, Garner A. Hydrocephalus, agyria, pseudoencephalocele, retinal dysplasia and anterior chamber anomalies. *J Med Genet* 1981; **18**: 314–7.
- 9 Warburg M. Hydrocephaly, congenital retinal non-attachment and congenital falciform fold. *Am J Ophthalmol* 1978; **85**: 88–94.
- 10 Warburg M. The heterogeneity of microphthalmia in the mentally retarded. *Birth Defects* 1971; **7**: 136–54.
- 11 Lahav M, Albert DM. Clinical and histopathologic classification of retinal dysplasia. *Am J Ophthalmol* 1973; **75**: 648–67.
- 12 Levine RA, Gray DL, Gould N, Pergament E, Stillerman ML. Warburg syndrome. *Ophthalmology (Rochester)* 1983; **91**: 1600–3.
- 13 Yanoff M, Rorke LB, Allman MI. Bilateral optic system aplasia with relatively normal eyes. *Arch Ophthalmol* 1978; **96**: 97–101.
- 14 Weiter JJ, McLean IW, Zimmerman LE. Aplasia of the optic nerve and disk. *Am J Ophthalmol* 1977; **83**: 569–76.
- 15 Whinery RD, Blodi FC. Hypoplasia of the optic nerve: a clinical and histopathologic correlation. *Ophthalmology (Rochester)* 1963; **67**: 733–8.
- 16 Quigley HA, Addicks EM, Green WR, Maumenee AE. Optic nerve damage in human glaucoma. II. The site of injury and susceptibility to damage. *Arch Ophthalmol* 1981; **99**: 635–49.
- 17 Waring GO III, Rodriguez MM, Laibson PR. Anterior chamber cleavage syndrome. A step ladder classification. *Surv Ophthalmol* 1975; **20**: 3–27.
- 18 Reese AB, Ellsworth RM. The anterior chamber cleavage syndrome. *Arch Ophthalmol* 1966; **75**: 307–18.
- 19 Johnston MC. The neural crest in abnormalities of the face and brain. *Birth Defects* 1975; **11**: 1–18.
- 20 Bahn CF, Falls HF, Varley GA, Meyer RF, Edelhauser HF, Bourne WM. Classification of corneal endothelial disorders based on neural crest origin. *Ophthalmology (Rochester)* 1984; **91**: 558–63.
- 21 Aymé S, Mattei JF. $HARD (\pm E)$ syndrome: report of a sixth family with support for autosomal recessive inheritance. *Am J Med Genet* 1983; **14**: 759–66.

Accepted for publication 24 January 1986.