# Optic nerve hypoplasia in infancy

**A R Fielder** FRCS **M I Levene** MD MRCP **J Q Trounce** MRCP **M S Tanner** MRCP
*Departments of Ophthalmology and Child Health, University of Leicester Medical School, Leicester*

**Summary**
Certain features of optic nerve hypoplasia (ONH), its systemic associations and investigation are exclusive to infancy. These include the facility to use cranial ultrasound, difficulties in assessing ocular features and visual function, and neonatal hypoglycaemia and jaundice. Six infants with ONH are presented; cerebral abnormalities were demonstrated by cranial ultrasound in five. Neonatal cholestatic jaundice and hypoglycaemia occurred in one infant. Two died and represent a group likely to remain undetected unless routine ophthalmic examination of neurologically abnormal neonates is undertaken. In infancy, both ocular and systemic aspects of ONH can be investigated simply and without sedation.

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## Introduction

Hypoplasia of the optic nerve is a relatively common congenital anomaly. Optic nerve hypoplasia (ONH), particularly if bilateral, can be associated with a large variety of ocular or systemic abnormalities[1-4]. As neuroendocrine dysfunction can occur with or without a structural neurological anomaly, Skarf and Hoyt[4] stated that CT scanning is not indicated unless the child shows clinical evidence of either hormone deficiency or a congenital anomaly. This approach may be satisfactory for clinical management of the older child or adult, but is not ideal for the neonate in whom it is important to determine the full extent of neurological involvement in order to anticipate any future developmental problems. Furthermore, appreciation of the full spectrum of congenital defects occurring in association with ONH permits a greater understanding of its pathogenesis.

In this paper we present the details of 6 infants with bilateral ONH who were seen in early infancy. Important aspects of investigation and clinical features exclusive to this age will be discussed. The emphasis is on noninvasive methods of investigating both ophthalmic and possible structural neurological anomalies, using electrodiagnosis, indirect video-ophthalmoscopy and cranial ultrasound.

## Methods

Six infants with bilateral ONH who presented over a two-year period to the Leicester Royal Infirmary have been studied. Cranial ultrasound was performed in coronal and parasagittal planes through the anterior fontanelle using an ATL 300i real-time scanner with a 3.5, 5 and 7.5 MHz multifrequency transducer. The lateral resolution of the 5 MHz and 7.5 MHz crystals are 1.6 and 0.9 mm respectively. Electroretinography (ERG), using skin or gold-foil electrodes, and visual evoked potentials (VEP) to a flash stimulus were performed as described previously[5]. Video-ophthalmoscopic recordings were obtained from two infants. All investigations were performed without sedation.

## Case reports

*Case 1:* A Caucasian boy, born at 38 weeks' gestation with a birthweight of 3.8 kg, was the first born child of unrelated parents. His mother was aged 25 at the time of delivery. Pregnancy was uneventful except for a urinary tract infection treated with ampicillin three weeks before the normal delivery. The neonatal period was complicated by hypoglycaemia, cyanotic attacks and hypothermia. At two months of age he was investigated because of cholestatic jaundice and hepatosplenomegaly, with elevated conjugated bilirubin (35 μmol/l), total bilirubin (336 μmol/l), and gamma-glutamyl transpeptidase (555 iu/l, normal <50 iu/l). No infective or metabolic cause was found for this hepatitis, which resolved spontaneously. At about this time he was noted to have nystagmus, and to be blind. Ophthalmoscopy revealed bilateral severe ONH. The skin electrode ERG was normal but the VEP to a flash stimulus was grossly reduced. No septum pellucidum was seen on either cranial ultrasound examination (Figure 1) or CT scan.

Growth velocity has remained normal, and there is no evidence of pituitary hypofunction. Unstimulated serum growth hormone at 18 months of age was 2.2 miu/l. Serum thyroxine was borderline low at 2 months of age (51 nmol/l, normal 54–142 nmol/l) but normal at three months (59 nmol/l) and 18 months (86 nmol/l), with normal TSH values throughout (4.6,

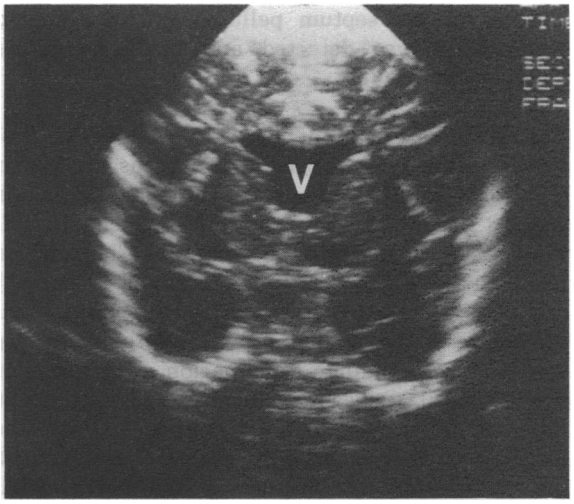


*Figure 1. Coronal ultrasound scan of Case 1 showing complete absence of the septum pellucidum with some ventricular dilatation* (V)

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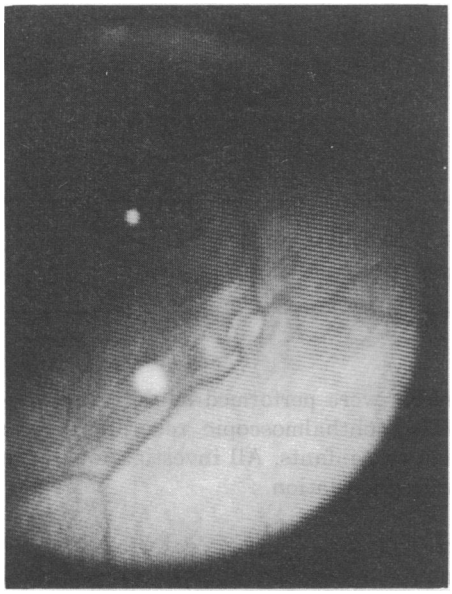

*Figure 2. Video-ophthalmoscopic recording of severe optic nerve hypoplasia in Case 2*

6.6 and 3.5 miu/l respectively). Serum cortisol concentrations rose appropriately after tetracosactrin acetate (Synacthen) – 133 nmol/l before, 416 nmol/l after – and exceeded 1100 nmol/l during a febrile convulsion at two years of age.

*Case 2:* A Caucasian male infant, born at term with a birthweight of 3.4 kg, was the product of healthy unrelated parents and pregnancy and delivery were normal. His mother was aged 28 years and this was her first child. The neonatal period was uneventful. He presented at three months of age with severely reduced vision, and ocular examination revealed gross bilateral ONH (Figure 2). The ERG was normal but the flash VEP was flat. Cranial ultrasound was normal.

*Case 3:* A Caucasian boy, born at term with a birthweight of 3.6 kg, was the first child of an 18-year-old mother. Pregnancy was normal except for hypertension just before the normal delivery. He presented at 10 weeks of age with severely reduced vision. Ophthalmoscopy revealed gross bilateral ONH. The ERG was normal but no VEP could be elicited. Cranial ultrasound and CT scan both revealed an absence of the septum pellucidum. No systemic abnormality was detected and blood endocrine levels were normal.

*Case 4:* A female infant, born after 38 weeks' gestation with a birthweight of 3.8 kg, was the fourth child of unrelated Asian parents; her mother's age was 38 years. The pregnancy had been normal. Floppiness was noted in the neonatal period and the head was enlarged. Cranial ultrasound (Figure 3) and CT scan (Figure 4) demonstrated a large fluid-filled cavity and a diagnosis of hydranencephaly was made. Ophthalmic examination at two days of age revealed up-beat nystagmus and significant bilateral ONH. A ventriculoperitoneal shunt was inserted at four months due to accelerated head growth. Despite serious ocular and neurological abnormalities, visual fixation developed although the vision remains poor. No VEP could be elicited; the ERG was not measured.

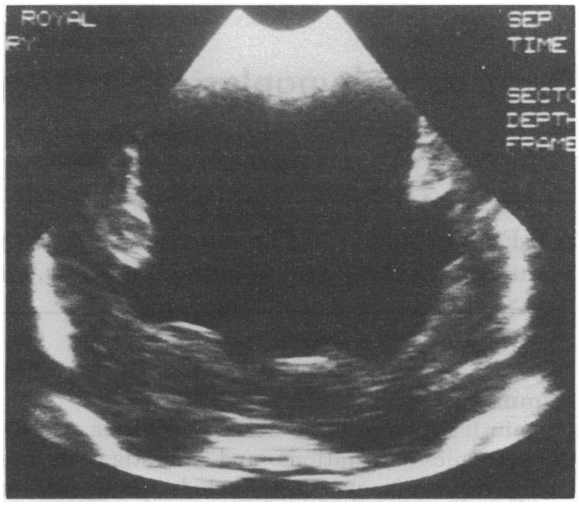


*Figure 3. Coronal ultrasound scan in Case 4 showing a large echo-free CSF-filled central cavity: hydranencephaly. The residual cerebral mantle shows no recognizable structures*

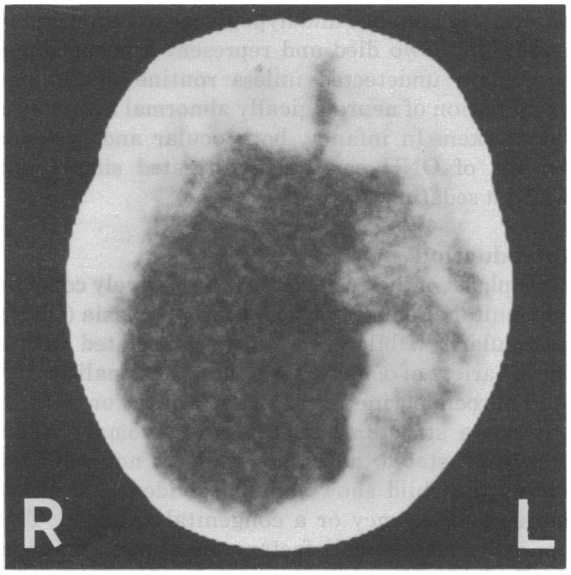


*Figure 4. CT scan from Case 4 showing the large fluid-filled cavity and surrounding cerebral tissue, more evident on the left side*

*Case 5:* A female Caucasian infant, born at term with a birthweight of 2.7 kg, was the first-born infant and her mother's age at delivery was 27 years. Pregnancy was normal but a lower segment caesarean section was performed for breech presentation. She suffered severe birth asphyxia and fits began on the first day of life complicated by a severe hypotensive episode. On ophthalmic examination at six weeks, horizontal nystagmus on horizontal versions was noted. A moderate degree of bilateral optic nerve hypoplasia and atrophy was observed. ERG and VEP were not performed. Ultrasound (Figure 5) and CT examinations showed subcortical cysts associated with cystic subcortical leucomalacia[6]. Her neurological condition deteriorated and she died at three months of age. At autopsy the brain was found to be atrophic with multiple subcortical cysts.

*Case 6:* An Asian female full-term infant, with birthweight 2.7 kg, was the first product of a non-consanguineous marriage; her mother's age was 28 years. Pregnancy and delivery were normal. There was a central cleft palate, hare lip and abnormal

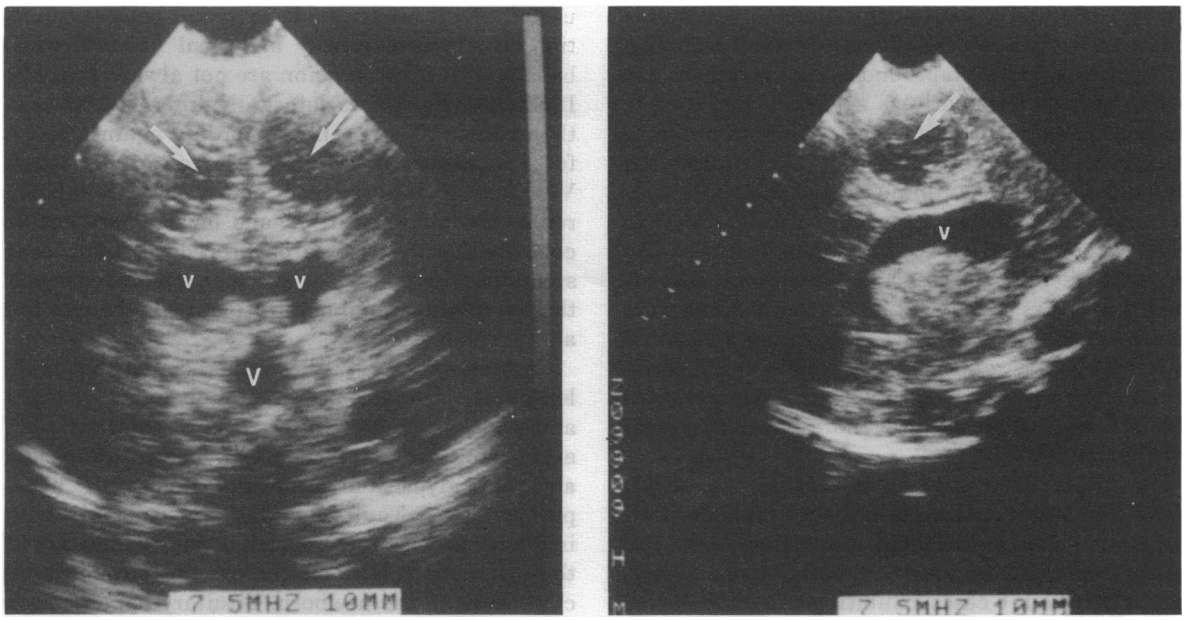


*Figure 5. Coronal (left) and parasagittal (right) ultrasound scans of Case 5 with cystic subcortical leucomalacia, showing minimally dilated lateral* (v), *third* (v) *ventricles and bilateral subcortical cysts (arrowed). (Reproduced from* Archives of Diseases in Childhood[6], *with kind permission)*

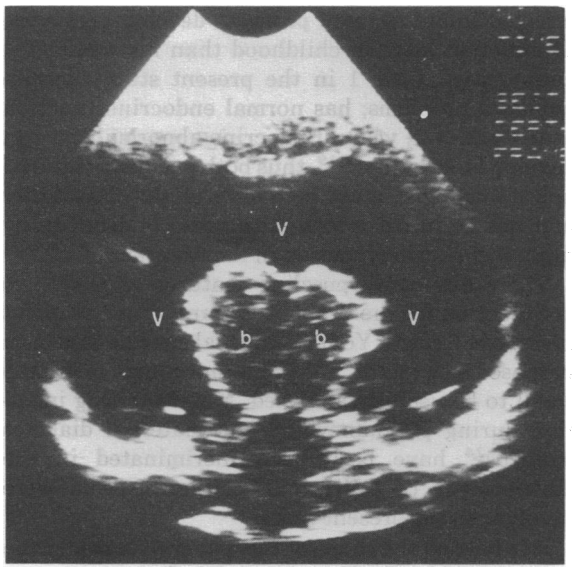


*Figure 6. Coronal ultrasound scan in Case 6 showing a dilated single ventricle* (v) *at the level of the basal ganglia* (b), *consistent with holoprosencephaly*

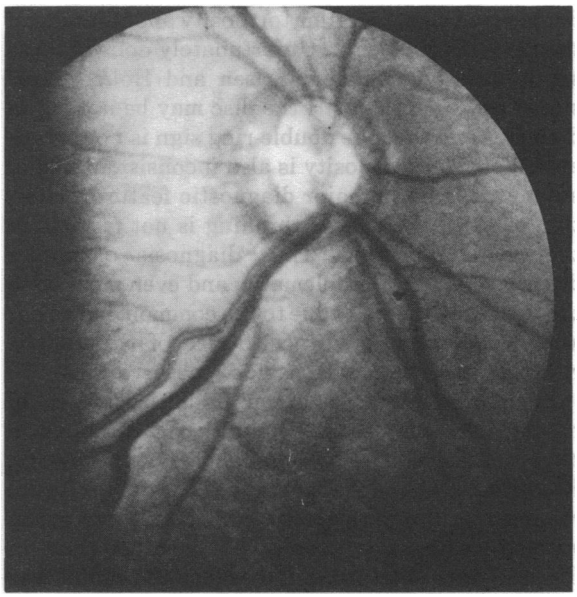

*Figure 7. Optic nerve hypoplasia: the disc appearance of Case 6 with holoprosencephaly*

facial appearance. Diagnosis of holoprosencephaly was made by cranial ultrasound (Figure 6). Severe bilateral ONH was diagnosed on the third day of life (Figure 7). Electrodiagnostic tests were not performed. Convulsions developed and she died at the age of three weeks. Autopsy was not performed.

## Discussion

These 6 cases give some indication of the variety of neurological abnormalities associated with ONH, but are not fully representative of the spectrum of ONH and its ocular and systemic associations, as only one mild (Case 5) and no unilateral cases have been included. Of the 3 who presented in infancy with poor vision (Cases 1, 2 and 3), one has no demonstrable structural anomaly of the neurological system, but 2 have septo-optic dysplasia (Cases 1 and 3). The 3 detected on routine ophthalmological examination of neurologically abnormal neonates (Cases 4, 5 and 6) exhibited more serious malformations: hydranencephaly, holoprosencephaly and cystic subcortical leucomalacia. As 2 of these died very early on, they represent a group of infants with severe neurological abnormalities in whom ONH may be present yet remain unrecognized unless such examinations are undertaken.

Certain clinical features of ONH, its systemic associations, and aspects of their investigation are exclusive to infancy. These include difficulties in the investigation of the ocular features and assessment of visual function, neonatal hypoglycaemia and jaundice. In addition, the investigation of cerebral structure is possible in infants by means of real-time ultrasound examination through the anterior fontanelle[7].

The value of cranial ultrasound is now recognized by paediatricians, but the ophthalmologist may be less well aware of this technique and not yet appreci-

ate its value as a neuro-ophthalmic investigative tool in infancy. It has the advantage of not requiring sedation and, being simple and quick to perform, can be repeated as frequently as necessary and used to study a changing situation. Ultrasound can only be utilized in infancy before the cranial sutures are closed, usually at about nine months of age. To date there are no reports on the use of ultrasound in ONH, although our cases clearly indicate that it can be used to identify the associated neurological structural anomalies. In 4 cases in which CT scans were also performed (Cases 1, 3, 4 and 5) no additional information was gained, and in our opinion ultrasound is the method of choice for the investigation of possible cerebral structural abnormalities of infants with this condition.

The major aspects of investigating the ocular and visual features of an infant with possible ONH are ocular examination and electrodiagnosis. The ophthalmoscopic diagnosis of ONH is not always easy. Five of our 6 cases exhibiting a marked degree of hypoplasia presented no difficulty. However, in one infant (Case 5) the hypoplasia was less severe, and as there was also concomitant optic atrophy the diagnosis was not so straightforward. Characteristically the disc is small, there is a peripapillary double-ring sign, vascular tortuosity and thinning of the nerve fibre layer[4,8]. Unfortunately none of these signs is pathognomonic; Frisen and Holmegaard[8] stated that in mild ONH the disc may be normal in diameter and that the double-ring sign is not invariable. Vascular tortuosity is also inconsistent and in any event is not a major diagnostic feature. Detection of nerve fibre layer thinning is not feasible in the neonatal period. Thus diagnosis of milder degrees of ONH is problematic, and even more so in the premature neonate due to the common, but to our knowledge unreported, occurrence of the double-ring sign in these babies (personal observation).

Examining the eyes of an infant suspected of having ONH may require anaesthesia, although in most instances this is probably not necessary. Recording the fundal appearance is useful for future reference, although photography in this age group without sedation is usually not possible (that in Figure 7 was obtained only because the infant was moribund and heavily sedated in order to prevent fits). The recently introduced video attachment to an indirect ophthalmoscope hopefully will help in this respect. Undoubtedly there is loss of clarity, especially during the process of obtaining still pictures from the television (Figure 2), and at this stage of development tape-playback is preferable for viewing. Video-ophthalmoscopy does, however, permit the simple and rapid recording not only of the posterior pole of the eye but also of the peripheral retina, usually a photographically inaccessible region. An added and unexpected advantage of video is that it can be used to demonstrate to parents the ocular abnormality.

Ophthalmic electrodiagnosis, as practised in most clinical centres, has a distinct but modest role. Both ERG and VEP can be recorded without sedation[5,9]. The ERG is clearly helpful in distinguishing between retinal and optic nerve involvement if the diagnosis of an infant with poor vision is in doubt. The VEP to a flash stimulus is of limited value in that it cannot be used to assess visual acuity, but the qualitative assessment of the response can be a useful, albeit crude, guide to visual pathway function in a neurologically abnormal neonate when behavioural tests of vision are not always possible. It may also be used to detect any difference between the eyes, or as a baseline recording against which future changes can be judged. The role of the pattern VEP for the assessment of acuity in early infancy remains controversial[10,11] and must at present be considered only a research procedure. Whichever stimulus type is used, it is important to remember that in infancy rapid maturational EP changes are also occurring.

Only recently has it been appreciated that problems in the neonatal period, notably hypoglycaemia and jaundice, are genuine associations of ONH[12-15], as in our Case 1[16]. Neonatal hyperbilirubinaemia and hypoglycaemia are associated with hypopituitarism[17]. Thyroxine and cortisol are both involved in bile salt excretion, and deficiency of these hormones may exacerbate the physiological cholestasis of the newborn. Pituitary hypofunction was not demonstrated in Case 1, however, and his liver dysfunction is unexplained. The natural history of neuroendocrine involvement in ONH is not clearly defined; although neonatal hypoglycaemia and jaundice settle, it is not known whether the affected infant is more prone to develop endocrine dysfunction later in childhood than his unaffected counterpart. Case 1 in the present study, despite neonatal problems, has normal endocrine function at the age of $2\frac{1}{2}$ years. Endocrine abnormalities can develop later in life[18,19], thus both paediatrician and ophthalmologist must be aware of this possibility and not be lulled into a false sense of security by normal endocrine function in the first year of life.

There are many puzzling features of ONH. Its predilection for the first-born infant[3,20] is borne out in 5 of our 6 cases. Young maternal age has also been proposed as a factor[4,20-22], but our numbers are too small to be usefully analysed. Maternal drug ingestion during pregnancy[22,23] and maternal diabetes mellitus[24] have both been incriminated in the development of ONH, but neither aspects were involved in the present cases.

It is beyond the scope of this paper to consider the pathogenesis of ONH in detail, but Case 5 raises an intriguing problem. This infant suffered neonatal hypoxic-ischaemic brain injury resulting in cystic subcortical leucomalacia[6]. It therefore has to be postulated either that ONH predated – and is unrelated to – the neurological abnormality, or that ONH can result from a neonatal insult. Frisen and Holmegaard[8] suggested that 'optic nerve hypoplasia can be viewed as a non-specific manifestation of damage to the visual system, sustained any time before its full development'. No conclusions can be drawn from one example, but according to this hypothesis the degree of hypoplasia would be expected to be greater the earlier the insult. It is pertinent to note that one infant in the present study (Case 5), who suffered birth asphyxia, exhibited only a moderate degree of ONH, although whether clinically visible hypoplasia could have developed in the six weeks between birth/insult and examination is unknown. Cerebral atrophy which may result from a variety of pre- and postnatal insults has been associated with ONH[25]. The possible influence of neonatal events in the genesis of ONH merits further study.

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*(Accepted 6 August 1985. Correspondence to ARF, Department of Ophthalmology, Clinical Sciences Building, Leicester Royal Infirmary, Leicester LE2 7LX)*