

MINI REVIEW

Optic nerve hypoplasia in children

Abstract

Optic nerve hypoplasia (ONH) is characterised by a diminished number of optic nerve fibres in the optic nerve(s) and until recently was thought to be rare. It may be associated with a wide range of other congenital abnormalities. Its pathology, clinical features, and the conditions associated with it are reviewed. Neuroendocrine disorders should be actively sought in any infant or child with bilateral ONH. Early recognition of the disorder may in some cases be life saving.

Optic nerve hypoplasia (ONH) is a non-progressive congenital abnormality of one or both optic nerves associated with a diminished number of axons in the involved nerve(s)^{1,2} with normal development of supporting tissues and the retinal vascular system. It gives rise to varying degrees of defective vision ranging from minimal visual impairment (with almost any type of visual field defect) to total blindness. It is now apparent that ONH often occurs in association with several clinically important endocrine and central nervous system (CNS) abnormalities.³ Ophthalmologists are in a unique position to suspect these conditions so that appropriate investigations and therapy can be initiated. ONH should be suspected in any patient with long-standing non-progressive impairment of vision of indeterminate cause. Segmental ONH⁴ and tilted discs in association with ONH⁵ have also been described, thus widening the concept of ONH into a larger group of syndromes. However, for the purpose of regarding ONH as a single entity such cases should probably be considered under a different heading.

Histopathology

Histologically a reduced number of optic nerve fibres can be demonstrated in a smaller than normal optic nerve. The retinal nerve fibre layer is diminished, the ganglion cells are reduced in number, but the outer retinal layers appear normal.¹ The area surrounding the small optic disc may be filled by an overgrowth of retinal pigment epithelium past the normal point of its termination, which gives rise to the 'double ring sign.'¹

Pathogenetic mechanisms

The pathogenesis of ONH is not fully understood. The formation of the retina takes place by differentiation of the inner and outer neuroblastic layers. The retinal ganglion cells and nerve fibres develop from the inner neuroblastic layer and appear early, while photoreceptors are the last structure to develop.⁶ The ganglion cells differentiate from the inner neuroblastic layer at the 17 mm embryonal stage.⁷ The axons grow centripetally and penetrate the mesodermal tissue of the primitive optic disc to form the neural elements of the optic nerve.

Failure of differentiation of the retinal ganglion cell layer between the 12 and 17 mm stages of embryonal development has been suggested as a cause of ONH.^{1,7,8} However, this theory implicates selective failure of growth of retinal ganglion cells. This is unlikely, since amacrine and hori-

zonal cells develop from the same precursor neural cells and develop normally in ONH.^{1,9,10} Moreover, as ONH is associated with other brain deformities, a pathogenetic mechanism must be proposed which explains the development of such multifocal pathology.

Other mechanisms which have been suggested include stretching of the optic nerve during development of abnormal cerebral hemispheres¹¹ and, in anencephaly, inadequate target organs which block the development of ascending pathways.^{11,12} The fundoscopic sign of homonymous hemioptic hypoplasia has been described in three patients with congenital hemiplegia and hemianopia, implicating retrograde axonal degeneration in each optic nerve.⁴

Recent embryological research has shown that overdevelopment of retinal ganglion cells is normally followed by a more than threefold cell death or 'apoptosis,' with consequent axonal degeneration within the optic nerve.¹³ It is therefore possible that excessive axonal regression culminates in ONH.

Aetiology

Little is known about the factors which predispose to ONH. It appears that an insult to the developing optic nerve on or around the 17 mm stage of embryonal development results in optic nerve hypoplasia. A number of teratogenic factors have been suggested. One series of 17¹⁴ and another of four patients¹⁵ have implicated maternal diabetes mellitus as an aetiological factor, but no prospective assessment has yet been carried out.

Postmaturity has also been reported.¹⁶ In one series of 20 cases of ONH nine patients (45%) had been born postmature, but only one had been born premature.

The development of ONH may also be related to young maternal age.¹⁷ In one series of 51 cases the mean maternal ages for ONH and a control group were significantly different at 22.1 years and 25.1 years respectively.¹⁸ Young maternal age has also been reported in association with septo-optic dysplasia, with septo-optic-pituitary dysplasia, and with isolated optic nerve hypoplasia.^{17,19} It is, however, possible that this association stems from a higher incidence of drug abuse among these young mothers rather than from low maternal age as such.²⁰

ONH may also be more common in first born children than later born.^{18,21,23} The reason for this is not apparent.

ONH has been reported in 48% of cases of fetal alcohol syndrome,²⁴ suggesting that alcohol is a major teratogen to the developing optic nerve. In that study a hypoplastic optic disc was defined as a size equal to or less than 2.07 mm,² with the fundoscopic signs of a double ring with sharply defined margins. However, it could not be ruled out that some mothers might also have used psychopharmaceutical drugs during pregnancy. An admitted history of alcohol abuse was obtained in 12.5% of mothers of children affected by the disorder.²³ Maternal use of anticonvulsants,²⁵ quinine,²⁶ lysergic acid diethylamide (LSD),²⁷ and phencyclidine²⁸ during pregnancy have been associated with optic nerve hypoplasia.

It is possible that smoking during pregnancy might have a



Figure 1: Appearance of the optic disc in optic nerve hypoplasia.

similar effect on the developing fetus, but there has been no study which has sought the appropriate data.

An autosomal dominant trait has been implicated in one family with five affected members,²⁹ but for the other reported cases insufficient data have been available to implicate a specific inheritance pattern.

Cytomegalovirus infection during pregnancy has been implicated as a cause of impaired optic nerve development in four infants.³⁰

Clinical features

Optic nerve hypoplasia may be seen in three situations: (1) as an isolated abnormality in an otherwise normal eye; (2) in grossly malformed eyes; (3) in association with a heterogeneous group of disorders most commonly involving the midline structures of the brain.

The degree of hypoplasia in ONH can vary considerably as can the clinical signs. In severe cases the diagnosis is clearly apparent. The small optic disc(s) and the double ring sign (Fig 1) are the hallmarks of the severe condition. The double ring sign indicates that a small nerve is present within the confines of a wider scleral canal. In less marked cases the diagnosis is reached first by clinical suspicion and the subsequent measurement of the relative and absolute size of the disc (see below). Abnormal visual fields and nerve fibre layer photographs provide additional supportive evidence for the diagnosis.

Bilateral disease has increasingly been reported as more common than unilateral disease.^{10 20 23 31} The incidence of ONH in males and females is equal.^{21 23 31} Asymmetrical as well as severe unilateral ONH commonly presents with concomitant squint. These cases are often misdiagnosed as primary squint. Trial of occlusion therapy is worthwhile in early childhood, as there may be treatable superimposed amblyopia.³² Moreover, ONH may leave the papillomacular bundle more or less intact.³³ Bilateral severe cases of ONH usually present with nystagmus or poor vision. A patient with ONH may have normal visual acuity but have visual field defects that pass undetected until later in life. Patients may also present because of the associated neuroendocrine abnormalities.³¹

Visual acuity

Impairment of visual acuity in ONH is variable. It can thus be difficult to assess the visual potential of a child with ONH on the basis of the appearance of the disc alone.^{3 34 35} Cases of ONH with normal visual acuities but with considerable defects in the inferior segments of the visual fields have been

reported.^{32 33} As such patients have no difficulties in work or other daily activities, the discovery of visual field defects may lead to the late diagnosis of ONH in patients with normal visual acuity. Such defects can raise the erroneous suspicion of neurological disease and may lead to unnecessary investigation.^{33 36}

PUPILLARY LIGHT REACTIONS

Careful assessment of the pupillary light reflex is very important in suspected cases of ONH, since there is usually some demonstrable degree of afferent pathway defect. This includes cases with normal visual acuity but with extensive field defects. In unilateral or asymmetrical cases the Marcus-Gunn pupil can be elicited.

REFRACTION

In 40 eyes reported on in which the refractive state has been recorded the spherical and cylindrical components were distributed as in the general population.³⁷

OPHTHALMOSCOPIC FINDINGS

The small size of the optic disc may be apparent on funduscopy. However, careful study of fundus photographs is recommended in all cases for which the diagnosis is uncertain, or when the degree of the optic nerve abnormality is in doubt.^{31 34 38} A slightly raised and blurred appearance of the optic disc margin characterises the normal appearance.²⁴ In hypoplastic optic discs there is a diminished number of nerve fibres at the disc border which may account for the sharply defined margins.³⁹ The commonest change seen round the optic disc is the presence of a circumpapillary halo, the size of which usually corresponds to that of the normal disc.³⁷ This gives rise to the appearance commonly described as the 'double ring sign.' The halo seen round the disc may be pigmented or non-pigmented and circumferential or partial.³⁷

The macula may show a flattening of the normal contours and loss of the foveal light reflex.⁴⁰ These changes are due to the relative absence of nerve fibres, the paucity of which can be discerned with red-free light.

The retinal vessels are usually of normal appearance, as the mesodermal elements are not involved. However, retinal vascular tortuosity has been reported in association with ONH.⁴¹

VISUAL FIELDS

Visual field defects are only occasionally described in ONH, mainly because most patients are too young for accurate perimetry. However, in 17 patients with ONH in whom the fields were tested it was shown that the commonest visual

TABLE I The neurological conditions associated with optic nerve hypoplasia

Condition	References
Porencephaly	10, 64
Cerebral atrophy	9
Microencephaly	
Anencephaly	79
Hydrocephaly	18
Hydranencephaly	1, 18
Perinatal encephalopathy, cerebellar atrophy, cerebral palsy, mental retardation, and cerebral infarcts	18
Encephaloceles	10
Colpocephaly	80
Basal encephalocele	81
Congenital suprasellar tumours	53, 82
Occasionally congenital third, fourth and sixth nerve palsies and up-gaze palsy	83
Behavioural problems	18

field abnormalities comprised bitemporal defects (seven cases) and generalised constriction (six cases).²³ Bitemporal hemianopia in ONH may be a helpful sign to detect the presence of midline defects of the central nervous system (CNS).^{11, 42}

Other authors have reported another 17 patients with segmental ONH and good visual acuity who were all the offspring of diabetic mothers; most had bilateral inferior altitudinal visual field defects which spared fixation.¹⁴ Several other forms of visual field defects have been reported, including binasal defects, small arcuate defects, and centro-caecal scotomata.³⁴ The relationship of the pattern of the field defects to the underlying cause or association has not been established.

COLOUR VISION

Colour vision testing has been performed in one case and was reported as being abnormal.²¹ No information was given on the nature of the abnormality. Colour visual function has been mentioned in only one other patient who had bilateral ONH, and it was reported as being normal in both eyes.⁴³

DIFFERENTIATION FROM HYPERMETROPIA

ONH should be differentiated from high hypermetropia, which may give a false impression of hypoplasia. Therefore the refractive state of the eye should always be assessed. The small optic disc may be difficult to diagnose, and clinical judgment is necessary in such cases, since there are no absolute criteria and no readily available techniques for accurate measurement. Ophthalmoscopic diagnosis of optic nerve hypoplasia may be equivocal in hypermetropic patients, in cases of bilateral mild hypoplasia, and in cases of subtle unilateral hypoplasia of the optic disc. In such cases red-free fundus photography with high resolution film can be used to examine the retinal nerve fibre layer for evidence of defects which correspond with the visual field loss.³⁹ However, many cases of ONH show a uniformly thin nerve fibre layer. This particular type of defect is much more difficult to define with certainty than are focal defects.⁴⁴

Absolute measurement of the size of the optic disc is difficult even in emmetropic eyes, because variation in size can substantially alter the total dioptric power despite no correction being required.⁴⁵ An alternative method is to compare the diameter of the optic disc with other measurable parameters in the same eye. But this assumes that the paired parameters bear a constant relationship to each other. The disc-macula: disc diameter ratio as measured from fundus photographs when greater than 3 indicates milder forms of ONH.⁴⁶⁻⁴⁸

The size of the disc image in fundus photographs is influenced by the anatomical dimensions of the eye, including the axial length, corneal curvature, and the shape of the fundus,⁴⁹ and by refractive errors and optical aberrations. The magnitude of these factors is generally not known for individual eyes. Absolute measurements may be achieved by using interference fringes to produce a scale on the optic disc,⁵⁰ but this method requires sophisticated instrumentation and a very co-operative patient.

Franceschetti and Bock⁵¹ measured the disc diameter by means of focal illumination of the fundus with a slit-lamp, using contact lens biomicroscopy with a micrometer scale. Estimation of the size of the optic disc by comparing the slit beam width on the Haag-Streit 900 slit-lamp with the optic disc on contact lens biomicroscopy has also been employed to measure hypoplastic optic discs.⁵² These 'measurements' are useful in comparing the diameter of the optic disc relative to the slit-lamp beam or the scale, as their magnification when projected on the optic disc is assumed to be the same as the

magnification of the optic disc, which is produced by the optical system of the eye. Comparing the size of the disc with the size of the whole part of the fundus as seen in the standard fundus photograph has also been suggested.⁵³ Indirect ophthalmoscopic measurement with a scale on the frontal or ocular lens has also been proposed.⁵⁴

Direct measurement of the orbital part of the optic nerve is possible by CT scanning. A-scan ultrasonography²³ and B-scan ultrasonography⁵⁵ may also be useful.

DIFFERENTIATION FROM OPTIC ATROPHY

ONH is sometimes incorrectly diagnosed as optic atrophy.³⁴ Although glial tissue usually imposes a rather pale colour on the disc in ONH,⁵⁶ the disc may be of normal colour. Red-free light ophthalmoscopy can be useful in delineating the area of the optic disc.

It has been suggested that non-progressive optic atrophy acquired any time before full development of the eye and the visual pathway, can produce a small atrophic optic disc which resembles that of ONH.³⁹

In an infant, examination with sedation or general anaesthesia, including fundus photography, may be required to differentiate ONH from optic atrophy. This differentiation is important in order to plan the investigation of the patient appropriately and also to provide adequate background data for counselling the parents.

RADIOLOGY OF THE OPTIC CANALS

Reduction in the size of the optic canals may be seen on x-ray.⁵⁷ The technique of axial tomography of the optic canals has been found more useful in this regard than plain foraminal views.⁵⁵ However, there is a significant range of normal diameters of the optic canal on each side which may result in a 20% difference in size.³⁸ There is no good correlation between ONH and the degree of diminution of the diameter of the optic canal as seen with optic foraminal projection.²¹

ELECTROPHYSIOLOGICAL FINDINGS

The electroretinogram and electro-oculogram in isolated ONH are normal, but the amplitude of the visually evoked response (VER) is commonly reduced. However, it appears that the VER is useful only as a correlate with the clinical assessment of vision.^{18, 58, 59} Severe bilateral cases of ONH which present in early infancy may need to be differentiated from conditions such as achromatopsia and Leber's amaurosis. In these cases the demonstration of a normal ERG response can be of critical diagnostic importance.

TABLE II *Ocular and systemic conditions associated with optic nerve hypoplasia*

Condition	References
Aniridia	84
Albinism	74, 85
High myopia	10
Chorioretinal and optic nerve head coloboma	56
Aicardi syndrome	86, 87
Potter's syndrome	88
Microphthalmos	83
Klippel-Trenaunay-Weber syndrome	89
Goldenhar-Gorlin syndrome	90
Duane's retraction syndrome	91
Hemifacial atrophy	38
Meckel syndrome	92
Blepharophimosis	93
Chondrodysplasia punctata	94, 95
Osteogenesis imperfecta	96
Deletion of the long arm of chromosome 13 (13q-)	97
Trisomy 18 'Edward's syndrome'	98
The syndrome of naevus sebaceus of Jadassohn	99
Midline facial defects including harelip, cleft palate, and hypertelorism	100

Associations of ONH

SEPTO-OPTIC DYSPLASIA

ONH is seen in 25% of cases of agenesis of the septum pellucidum.⁶⁰ Conversely, 27% of patients with ONH had partial or complete absence of the septum pellucidum.²³ This condition is known as septo-optic dysplasia. The neurological features of this condition are mental retardation, spasticity, abnormalities of taste, and impaired smell.⁶¹ However, some patients have only mild deficits, with normal intelligence.⁶¹ Ablation of the septum pellucidum in animals impairs their ability to learn tasks requiring spatial orientation.⁶² A spatial learning disorder in a 13-year-old girl with severe ONH and absence of the septum pellucidum has been reported.⁶³ It may therefore be useful to look for this lesion in such children so that they may get the best education.

OTHER NEUROLOGICAL ASSOCIATIONS

ONH is associated with a large number of other neurological disorders (Table I).

ENDOCRINOLOGICAL ASSOCIATIONS

Pituitary dysfunction arising as a consequence of hypothalamic maldevelopment may accompany septo-optic dysplasia.^{18 61 65 67} Moreover, ONH with a normal septum pellucidum may also be associated with hypopituitarism,⁶⁸ the degree of which may vary between subclinical disorder and panhypopituitarism. It is clearly important to establish the diagnosis in infancy so that optimal replacement therapy can be given.^{61 68} Since the coincidence of pituitary hypofunction and optic nerve hypoplasia was first reported in 1970,⁶⁹ the true incidence of hypopituitarism with ONH has not been determined in a large series of patients. Furthermore, unlike patients with idiopathic hypopituitarism, who commonly show delayed growth beginning at 6 to 15 months of age, children with septo-optic dysplasia and a deficiency of growth hormone frequently have normal growth until their third or fourth year of life.^{20 68} Diabetes insipidus has also been reported in association with bilateral ONH and in association with septo-optic dysplasia.⁷⁰ Necropsy on one patient who had bilateral severe ONH, hypopituitarism, and diabetes insipidus showed the cells of the supraoptic and paraventricular nuclei to be abnormally small and few in number.²² Pituitary dysfunction may also show as prolonged neonatal hyperbilirubinaemia, hypotonia, infantile hypoglycaemia without hyperinsulinaemia, hypothyroidism, and growth retardation.^{22 68 71} Pituitary dysfunction can complicate general anaesthesia, especially if it has not been recognised preoperatively.⁷² In one series of 93 cases of children with ONH hypothyroidism was the most frequent endocrine disturbance.¹⁰ This was an unexpected finding, in view of the frequently emphasised principal association of ONH and growth hormone deficiency.

NEURORADIOLOGICAL FINDINGS IN SEPTO-OPTIC DYSPLASIA

The anatomical defects of septo-optic dysplasia may be subtle, and an apparently normal septum pellucidum on CT does not invalidate a clinical diagnosis of a mild form of septo-optic dysplasia.⁷³ For cases of bilateral ONH a CT scan is usually indicated to exclude midline or other cerebral structural abnormalities.⁷⁴ In particular it has been recommended that children with bilateral ONH, nystagmus, and poor vision should undergo a thorough neuroradiographic and endocrine examination.²⁰ It has been shown that CT accurately delineates the altered anatomy of septo-optic dysplasia.⁷⁵ Enlargement of the pituitary stalk and infundibulum

may be seen when septo-optic dysplasia is associated with diabetes insipidus.⁷⁵ Dilated ventricles were also noted.^{66 76} Neuroradiographic abnormalities were reported in 39% of 41 children who had bilateral ONH, poor vision, and nystagmus.¹⁰ These abnormalities included absence of the septum pellucidum, absence of the corpus callosum, encephaloceles, porencephaly, and hemispheric atrophy.

Real time cranial ultrasound can be used in infants to image cerebral structures.^{77 78} Magnetic resonance imaging (MRI) has been used in the newborn to investigate intracranial structure and pathology. However, the role of MRI in cranial imaging of infants has not been clearly defined.⁷⁷

OTHER OCULAR AND SYSTEMIC ASSOCIATIONS

A large number of other systemic and ocular associations with ONH have been reported (Table II).

Conclusion

ONH should be sought in any child with poor vision or in patients labelled as having amblyopia resistant to occlusion. All children with ONH, particularly those with severe visual loss, and all bilateral cases with impaired vision, should have a careful clinical examination including a CT scan. The general physical examination of the child with special reference to height and weight may indicate the need for investigation of pituitary function and should be performed on all children with an abnormal CT appearance. The frequent association of CNS anomalies and endocrine problems with ONH is an important piece of information which the attendant ophthalmologist must convey to the paediatrician and the family practitioner, with a view to arranging appropriate and early treatment.

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