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Neuro-ophthalmology Update

Congenital anomalies of the optic nerve

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Abstract

Congenital optic nerve head anomalies are a group of structural malformations of the optic nerve head and surrounding tissues, which may cause congenital visual impairment and blindness. Each entity in this group of optic nerve anomalies has individually become more prevalent as our ability to differentiate between them has improved due to better characterization of cases. Access to better medical technology (e.g., neuroimaging and genetic analysis advances in recent years) has helped to expand our knowledge of these abnormalities. However, visual impairment may not be the only problem in these patients, some of these entities will be related to ophthalmologic, neurologic and systemic features that will help the physician to identify and predict possible outcomes in these patients, which sometimes may be life-threatening. Herein we present helpful hints, associations and management (when plausible) for them.

Keywords: Coloboma, Congenital, Optic disc excavation, Systemic anomalies, Optic nerve malformations

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Introduction

Congenital malformations of the optic nerve, especially those involving the optic nerve head and surrounding tissues, include a broad spectrum of malformations frequently associated with congenital blindness or significant visual impairment. [1] As a result of sensory deprivation (either unilateral or bilateral) infantile nystagmus or sensory strabismus may be present in patients affected by such abnormalities; in addition, superimposed amblyopia should be suspected (and treated) in those children.[2]

Each entity in this group of optic nerve anomalies has individually become more prevalent as our ability to differentiate between them has improved due to better characterization of cases.[3] Access to better medical technology (e.g., neuroimaging and genetic analysis advances in recent years) has helped to expand our knowledge of these abnormalities. However, visual impairment may not be the only problem in these patients, some of these entities will be related to ophthalmologic, neurologic and systemic features (especially endocrinologic disturbances) that will help the physician to identify and predict possible outcomes in these patients, which sometimes may be life-threatening.[4–6]

Optic nerve hypoplasia

Optic Nerve Hypoplasia (ONH) is the most commonly found optic nerve head anomaly.[3] It is a congenital, non-progressive, developmental anomaly characterized by the tetrad of: small optic disc, peripapillary ''double-ring sign'', thinning of the nerve fibre layer and vascular tortuosity. Patients with ONH should be assessed for systemic associations such as neurologic and endocrine abnormalities.[6] Neuroimaging findings include hypoplastic optic nerves with a hypoplastic chiasm, and other cerebral abnormalities. Abnormalities of

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the white or grey matter, hydrocephalus, septo-optic dysplasia (Fig. 1), and corpus callosum anomalies have been described.[7] ONH can be unilateral or bilateral and can account for 15–25% of children with significant congenital visual loss.[8] In addition, some investigators believe that foetal exposure to teratogenic agents like maternal alcohol and drug abuse has increased the incidence of the disease in recent years.[3] Superior segmental optic nerve hypoplasia with inferior visual field defects has been associated with the presence of maternal insulin-dependent diabetes.[9,10] Embryologically, an alteration in prenatal development during the sixth week and the fourth month of gestation is accounted for the decreased number of axons in the involved nerve.[11]

Visual acuity in patients with ONH does not necessarily correlate with the size of the optic nerve head as it correlates better with the integrity of the maculopapillary bundle.[7] It tends to be stable with time and other visual functions also may remain unaltered (e.g., colour vision). In some patients, visual acuity remains mainly unaffected and the finding of visual field defects later in life may result in a late diagnosis of congenital ONH. An afferent pupillary defect may be found in those patients with good visual acuity with significant visual field defects.[7]

The diagnosis of ONH is usually established clinically based on fundus examination of the optic disc that will show a small optic disc with very large vasculature.[12] In extreme cases, an area of bare sclera can be seen surrounding a hypoplastic pale disc. In more mild cases, disc to macula distance/disc diameter ratio will be increased. A ratio of 2.94 is seen in the normal population and greater than three indicates milder forms of ONH.[13] The ''double ring sign'' can be seen in some patients and is characterized by a pigmented ring surrounding the disc. Retinal vascular tortuosity is also an important but inconsistent sign. None of the above is considered pathognomonic.

ONH may have other congenital ocular associations such as microphthalmos, aniridia, coloboma, nystagmus and strabismus. Strabismus usually develops at 3 months of age if the condition is bilateral.[14] Commonly, ONH can be associated with neurological and endocrine abnormalities. Hormonal alterations include thyroid, growth, adrenal and antidiuretic hormone deficiencies. The risk of developing such deficiencies is increased in bilateral cases or if midline brain defects are present.[15] Milder hormonal alterations occur in unilateral cases. Borchert et al. showed also that bilateral abnormalities are also associated with a higher risk of hypothalamic/pituitary dysfunction and developmental delay.[16] A common neurological association is agenesis of septum pellucidum, condition knows as septo-optic dysplasia that leads to mental retardation and spasticity.[17] Other associations include anencephaly, cerebral atrophy, basal encephalocoeles, hypoplasia of the cerebellar vermis, cystic dilatation of the fourth ventricle, and posterior fossa cysts.[7,8,15]

Genetic associations include homozygous mutations in the *HESX1* gene that were found in children with septo-optic dysplasia.[18,19] Also, a number of familial cases have also been described with a number of mutations in developmental transcription factors including *SOX2*, *SOX3* and *OTX2* being implicated in its aetiology.[20,21] Mitochondrial disease may also be associated with ONH. Taban et al.[22] showed 10 cases of ONH in his series of 80 patients with non-syndromic mitochondrial cytopathies.

Physicians have to be aware of hypothalamic dysfunction and also order an MRI of the brain to rule out intracranial abnormalities.[23] Endocrine workup should include fasting morning cortisol and glucose, TSH, free T4, IGF-1, IGFBP-3 and prolactin.[7] In younger children luteinizing hormone, follicle-stimulating hormone, and testosterone levels should also be included to anticipate delayed sexual development.[7]

Excavated optic disc anomalies

Morning glory disc anomaly

Morning Glory Disc Anomaly (MGDA) is a term first used by Kindler [24] in 1970 to describe the resemblance of the optic nerve head malformation to a flower of the same name (family *Convolvulaceae*). An enlarged excavation, abnormal retinal vascular pattern, annular pigmentation surrounding the nerve head, and a characteristic glial tuft, give the appearance of the MGDA (Fig. 2). This condition is usually unilateral and can occur equally in males and females.[25] It has been determined that an embryonic development alteration of the lamina cribrosa and the posterior sclera causes this defect.[26] MGDA is usually sporadic and no specific genetic defect has been described in association with this anomaly.

Visual acuity in patients with MGDA is usually poor with only 30% achieving 20/40 or better.[27] Afferent pupillary defects and visual defects are often present, specially in unilateral disease.[28] Many ocular, facial and neurological associations have been described. Ocular findings such as optic nerve calcifications, glial tuft, microphthalmos and retinal detachment are frequent.[27,29] Facial abnormalities like hyper-

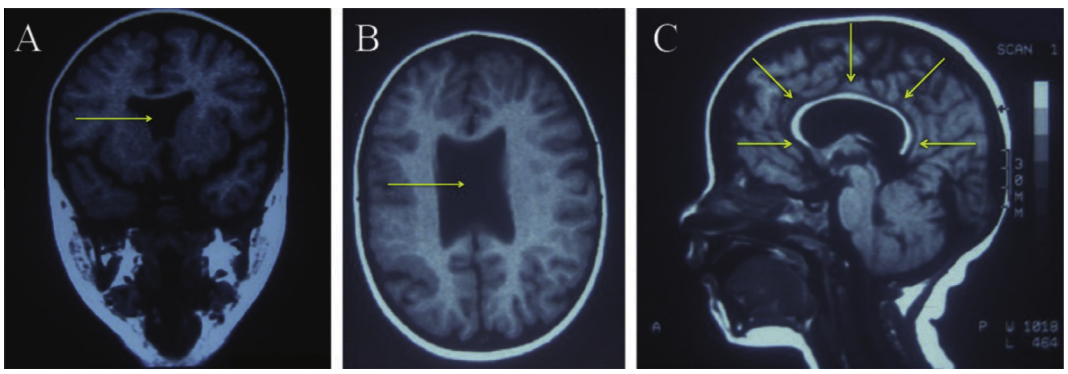

Figure 1. Septo-optic dysplasia (MRI). (A) and (B) Septum pellucidum agenesis (yellow arrow); and (C) corpus callosum atrophy (yellow arrows).