

# 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.<sup>1</sup> 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.<sup>2</sup>

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.<sup>3</sup> 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.<sup>4-6</sup>

## Optic nerve hypoplasia

Optic Nerve Hypoplasia (ONH) is the most commonly found optic nerve head anomaly.<sup>3</sup> 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.<sup>6</sup> 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.<sup>7</sup> ONH can be unilateral or bilateral and can account for 15–25% of children with significant congenital visual loss.<sup>8</sup> 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.<sup>3</sup> Superior segmental optic nerve hypoplasia with inferior visual field defects has been associated with the presence of maternal insulin-dependent diabetes.<sup>9,10</sup> 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.<sup>11</sup>

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.<sup>7</sup> 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.<sup>7</sup>

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.<sup>12</sup> 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.<sup>13</sup> 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.<sup>14</sup> Commonly, ONH can be associated with neurological and endocrine abnormalities. Hormonal alterations include thyroid, growth, adrenal and anti-diuretic hormone deficiencies. The risk of developing such deficiencies is increased in bilateral cases or if midline brain defects are present.<sup>15</sup> 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.<sup>16</sup> A

common neurological association is agenesis of septum pellucidum, condition known as septo-optic dysplasia that leads to mental retardation and spasticity.<sup>17</sup> Other associations include anencephaly, cerebral atrophy, basal encephaloceles, hypoplasia of the cerebellar vermis, cystic dilatation of the fourth ventricle, and posterior fossa cysts.<sup>7,8,15</sup>

Genetic associations include homozygous mutations in the *HESX1* gene that were found in children with septo-optic dysplasia.<sup>18,19</sup> 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.<sup>20,21</sup> Mitochondrial disease may also be associated with ONH. Taban et al.<sup>22</sup> showed 10 cases of ONH in his series of 80 patients with non-syndromic mitochondrial cytopathies.

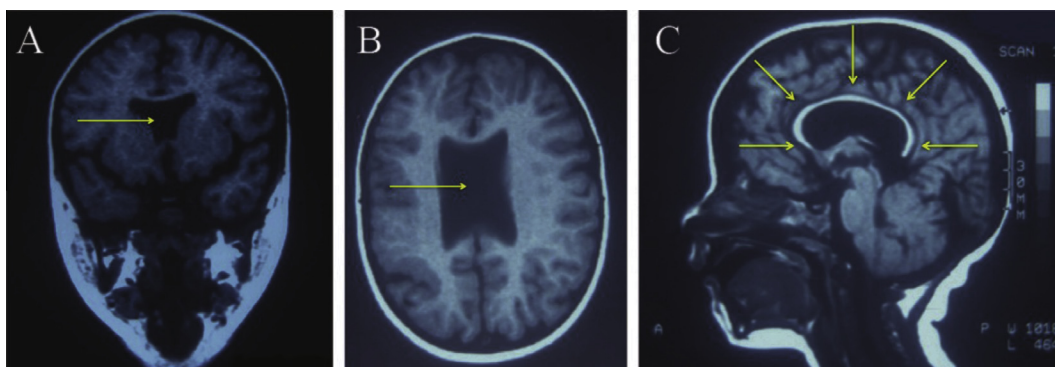
Physicians have to be aware of hypothalamic dysfunction and also order an MRI of the brain to rule out intracranial abnormalities.<sup>23</sup> Endocrine workup should include fasting morning cortisol and glucose, TSH, free T4, IGF-1, IGFBP-3 and prolactin.<sup>7</sup> In younger children luteinizing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

## Excavated optic disc anomalies

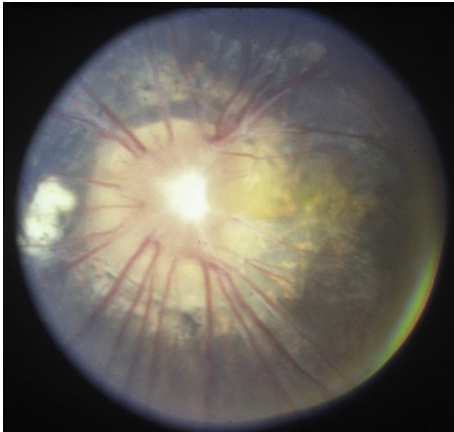
### Morning glory disc anomaly

Morning Glory Disc Anomaly (MGDA) is a term first used by Kindler<sup>24</sup> 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.<sup>25</sup> It has been determined that an embryonic development alteration of the lamina cribrosa and the posterior sclera causes this defect.<sup>26</sup> 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.<sup>27</sup> Afferent pupillary defects and visual defects are often present, specially in unilateral disease.<sup>28</sup> Many ocular, facial and neurological associations have been described. Ocular findings such as optic nerve calcifications, glial tuft, microphthalmos and retinal detachment are frequent.<sup>27,29</sup> 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).



**Figure 2.** Morning glory disc anomaly showing an enlarged excavation, abnormal retinal vascular pattern, annular pigmentation surrounding the nerve head and central glial tuft and peripapillary changes.

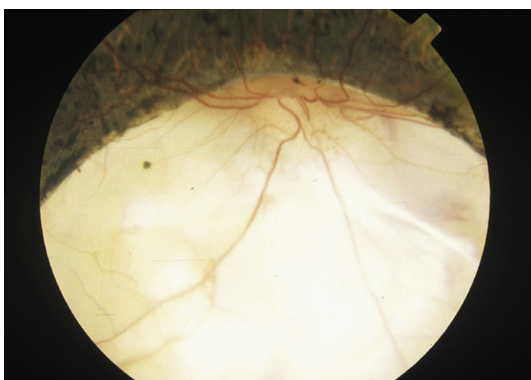
telorism, cleft lip and cleft palate are also described.<sup>6</sup> Central nervous system (CNS) defects like encephaloceles, agenesis of corpus callosum, and endocrine abnormalities have also been associated with MGDA. In 1985, Hanson et al.<sup>[30]</sup> first described the association of MGDA with Moyamoya disease, a cerebrovascular abnormality characterized by abnormal narrowing of the cerebral arteries. Since then, additional cases have been reported. For this reason, Moyamoya disease should always be evaluated in these patients.<sup>31</sup>

Management starts with a correct diagnosis; early amblyopia has to be addressed properly to optimize visual acuity.<sup>32</sup> Additionally, a complete evaluation of the CNS with MRI and CTA must be guaranteed.<sup>25</sup>

### Optic disc coloboma

A sharply demarcated white excavation that replaces part of the optic disc characterizes Optic Disc Coloboma (ODC) (Fig. 3). The prevalence has been reported to be 0.14% in the general population and the condition is usually sporadic. Half of the cases have bilateral involvement.<sup>33</sup> ODC usually involves the inferonasal aspect of the disc and can affect retina, uvea and sclera (Fig. 4).

Clinically, visual acuity can vary depending on the papillomacular bundle involvement. Ocular associations such as microphthalmos, iris coloboma, ciliary coloboma, lens notch-



**Figure 3.** Retinochoroidal coloboma involving the optic disc.



**Figure 4.** Nineteen-month-old girl with optic disc coloboma in her right eye (orbital CT).

ing, retinal detachment, neovascular membranes and macular holes have been described.<sup>5,33</sup> Retinal detachment is secondary to breaks in the vulnerable membrane that overlies the coloboma and where liquefied vitreous can enter thus dissecting the subretinal space. Pal et al.<sup>34</sup> showed that vitrectomy with silicon oil had a good success rate in patients with ODC and retinal detachment.

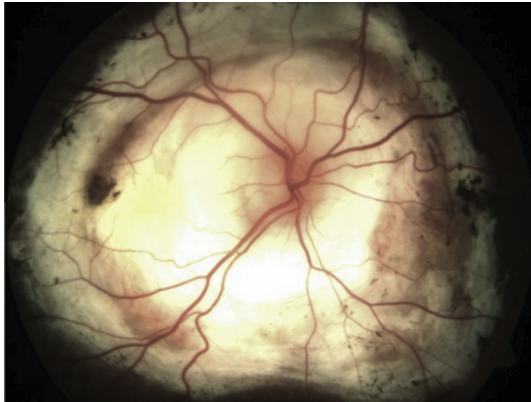
Systemic associations have also been described, such as the renal coloboma syndrome that can lead to an important renal failure degree and has been associated with the PAX2 mutation.<sup>35</sup> Other conditions like CHARGE association, Aicardi syndrome, Goldenhar sequence, and Walker-Warburg syndrome have also been associated with ODC.<sup>36-39</sup> Additional management in these patients includes use of sunglasses to reduce the photophobia and treatment for anisometric amblyopia in cases of low visual acuity.

### Renal coloboma syndrome

Renal coloboma syndrome (RCS), also called Papillorenal syndrome is an autosomal dominant disorder characterized by the triad of optic nerve dysplasia, renal and genitourinary malformations and progressive renal failure. The malformation tends to be bilateral.<sup>40</sup> As mentioned earlier, it has been associated with the PAX2 mutation specifically in 10q.<sup>35,41,42</sup> Coloboma is not the only optic nerve anomaly associated, MGDA and ODH have also been reported.<sup>40</sup> Renal findings include renal hypodysplasia and oligomeganephronia.<sup>43</sup> The association between optic disc dysplasia and renal dysplasia makes imperative a complete screening for kidney disease in patients with any excavated optic disc anomaly, and fundus examination in patients with renal hypoplasia.

### Peripapillary staphyloma

Peripapillary staphyloma (PS) is a rare, nonhereditary, and usually unilateral anomaly. It manifests as a deep excavation surrounding the optic disc (Fig. 5). The optic disc per se can appear normal, but in some cases pale regions can be appreciated. Visual acuity is usually low, and compared to other CODA is rarely associated with other congenital defects or systemic diseases.<sup>44</sup> Compared to MGDA, optic



**Figure 5.** Peripapillary staphyloma is shown as a deep excavation surrounding a normal optic disc.

disc and vessels are usually normal. Also, a deeper excavation is seen and the glial tuft is absent. Ocular associations include degenerative myopia but emmetropic patients have also been reported.<sup>45</sup> Kim et al.<sup>45</sup> showed patients with PS can achieve significant visual improvement by occlusion therapy. Regular follow-up of these patients is usually recommended.

### Megalopapilla

Described for the first time by Franceschetti and Bock<sup>46</sup>, megalopapilla is an anomaly that consists in an enlarged optic disc with normal disc morphology. Two phenotypes are described: the most common one is bilateral with optic disc diameter greater than 2.1 mm (Fig. 6). The second form is a unilateral form in which the normal optic cup is replaced by a gross excavation that obliterates the adjacent neuroretinal rim.<sup>47</sup> Case reports have documented that megalopapilla is associated with bigger than normal blind spots and occasionally reduced visual acuity.<sup>48</sup> It may be confused with severe cases of glaucoma because the cup area looks bigger in both conditions; however, disc area in megalopapilla is significantly larger in megalopapilla compared to glaucomatous eyes. In addition, advanced glaucoma is associated with a smaller rim area than megalopapilla.<sup>49</sup>

### Optic pit

First described by Wiethe<sup>50</sup> in 1882, Optic Pit (OP) is an excavation or regional depression of the optic nerve head.

The prevalence is less than 1 in 10,000 patients and it is considered to be bilateral in 10–15% of cases.<sup>51</sup> Histologically, an OP is seen as a dysplastic retina herniated posteriorly into a pocket defect in the lamina cribrosa.<sup>51</sup> In fundus examination, they look like a round excavation near the margin of the optic disc. Their size varies between a quarter and an eighth of the disc, and the colour of the pit can be yellow, grey or white.<sup>3</sup> Cilioretinal vessels can also be observed going in and out of the pit. Large temporal pits are associated with a higher risk of developing macular detachments but are not associated with the extension of such detachments.<sup>52</sup>

Visual symptoms usually begin when an associated serous macular elevation is present and are more frequent in the third and fourth decade of life. For this reason, asymptomatic patients begin to report decreased visual acuity of relatively fast progression. The degree of decrease in visual acuity depends in the extension of the schisis and sensory detachments. Prognosis will be affected by the duration of the lesions previously named.<sup>53</sup>

Diagnostic testing for this anomaly includes fluorescein angiography, fundus autofluorescence, optical coherence tomography (OCT) and visual fields. The most common defect seen in OP is arcuate scotoma but almost any visual field defect can be present due to the displacement of the nerve fibres.<sup>54</sup> Previous studies of serous macular detachment in OP have shown cases of both, spontaneous reattachment and persistent detachment.<sup>52,55</sup> Early surgical intervention such as juxtapapillary photocoagulation and vitrectomy have demonstrated the best chance at visual acuity improvement.<sup>51</sup>

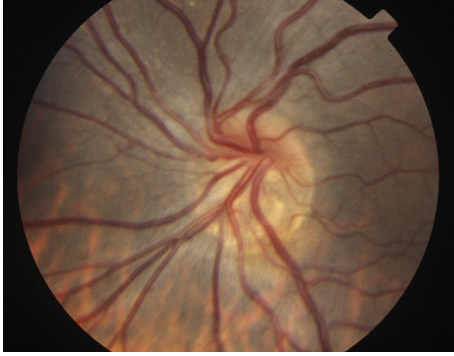
### Tilted discs and congenital tilted disc syndrome

Tilted disc (TD) is a condition where the optic nerve appears to enter the eye in an oblique angle. Its prevalence is reported to be around 0.4–3.5%, and bilateral cases are in a range of 37.5–80% of the patients.<sup>56</sup> Clinically, the optic nerve appears to enter the eye in an acute angle rather than perpendicularly, being the superotemporal part elevated and the inferonasal posteriorly displaced (Fig. 7). This results in an oval looking optic disc. The direction of this tilting is most common in the inferonasal direction.<sup>57</sup> Embryologically, TD is presumably related to a malclosure of the embryonic optic fissure.<sup>58</sup>

Ocular associations with patients with TD include refractive errors, colour vision alterations, visual field defects,



**Figure 6.** Bilateral megalopapilla phenotype. Optic disc and cup area are significantly enlarged.



**Figure 7.** Tilted disc with superotemporal part elevated and the inferonasal posteriorly displaced. Additionally, situs inversus of the vessels is present.

and retinal abnormalities. Chorioretinal thinning, posterior staphyloma, and peripapillary atrophy are common retinal findings.<sup>59</sup> The relation between tilted disc and glaucoma has been studied, The Tanjong Pagar Study concluded that both were not associated.<sup>60</sup>

Congenital tilted disc syndrome (CTDS) was first described by Fuchs<sup>61</sup> in 1882. It is a condition in which the optic disc appears tilted, usually inferonasally, and is associated with a thinning of the retinal pigment epithelium, posterior staphyloma and situs inversus of the retinal vessels.<sup>58</sup> Fuchs<sup>61</sup> described that the most common visual field defect found in patients with CTDS was a scotoma in the superior temporal quadrant.

#### *Congenital optic disc pigmentation*

Congenital Optic Disc Pigmentation (CODP) is an anomaly in which the optic disc has a greyish appearance secondary to melanin deposition anterior to the lamina cribrosa. True CODP is a very rare condition and very few cases have been reported.<sup>47</sup> Brodsky et al.<sup>62</sup> reported an association with a deletion of chromosome 17 in one patient. He described that his cases of grey optic discs in neonates were notable for the absence of visible pigmentation within the optic disc, resolution of grey discoloration in a few months, and development of albinotic features in some of the infants.

#### *Aicardi's Syndrome*

Aicardi's Syndrome consists of multiple clinical features such as infantile spasms or seizures, agenesis of the corpus callosum and multiple depigmented lesions called "chorioretinal lacunae" clustered around the disc. Associated excavated optic disc anomalies such as coloboma and ONH can accompany this syndrome.<sup>47</sup> Other frequent ocular associations described include microphthalmos, retinal detachment, iris colobomas and pseudogliomas. CNS anomalies include agenesis of the corpus callosum and other malformations such as colpocephaly and cerebral hemispheric asymmetry.<sup>37</sup>

#### *Myelinated nerve fibres*

First described by Virchow<sup>63</sup> in 1856, patients with myelinated nerve fibres (MNF) represent approximately 1% of the population.<sup>64</sup> Normal retinal nerve fibres are not myelinated. The visual pathway starts myelination at the fifth month of



**Figure 8.** Myelinated nerve fibres nasally to the disc producing flame-like patch of white colour.

gestation and ends at the lamina cribrosa at birth. A proposed pathogenesis for this malformation is an anomalous location of retinal oligodendrocyte glial cells that migrate before the formation of the lamina cribrosa.<sup>65</sup> Clinically, and in more ornate cases, MNF looks like a flame-like patch of white or yellow colour usually located near the upper or lower borders of the optic disc (Fig. 8). Visual defects can exist depending on the extension of the defect. Ocular associations like myopia and resistant amblyopia have also been reported.<sup>65</sup> Systemic associations include neurofibromatosis type 1 and craniofacial abnormalities.<sup>66</sup> Treatment of MNF consists in correcting the associated ocular pathology.

#### *Doubling of the optic disc*

Doubling of the optic disc is a very rare anomaly in which two discs appear to be one next to the other in the fundus examination. This occurs presumably from a division of the optic nerve into two fasciculi before entering the eye. Each disc has its own vascular system. Few cases have been reported but the condition is usually unilateral and associated with low vision.<sup>67</sup>

#### *Pseudopapilledema (optic disc drusen)*

The most common form of pseudopapilledema is secondary to buried drusen within the optic disc. Other causes are myelinated nerve fibres, epipapillary glial tissue and hyaloid traction on the disc.<sup>47</sup> Lorentzen et al.<sup>68</sup> reported a prevalence of 0.34% in his cohort of 3200 paediatric patients. In their study, there was an increased risk in children who had family members with drusen. Optic drusen are caused by a deposition of calcified axonal debris and are usually buried within the optic disc. Patients are usually asymptomatic but in extreme cases drusen can cause alteration in visual acuity and visual fields. Optic head drusen has also been associated with peripapillary retinal neovascularization and haemorrhagic complications in some cases.<sup>69,70</sup> Ultrasound is a good diagnostic method to evaluate patients who have blurred optic discs and in whom drusen are suspected.<sup>71</sup>

#### **Conclusions**

Congenital anomalies of the optic disc may occur in isolation or as part of a larger systemic malformation syn-

drome. Visual impairment or total blindness are frequently associated with most of the Congenital Optic Disc Anomalies, but the amount of visual limitation may be decreased by early detection and treatment of concurrent ocular abnormalities and refractive defects. Superimposed amblyopia is frequently found in patients with optic nerve head malformations and it should be addressed properly to guarantee the best visual outcomes.

A multidisciplinary approach will be the mainstay to assure good developmental results in children with optic nerve anomalies by detecting simultaneous abnormalities in other body systems (especially neurologic, endocrinologic and renal abnormalities). Such comprehensive medical approach will provide better expert care and it will help to avoid life-threatening complications.

Genetic and molecular basis of these anomalies are just begging to be characterized and have become an area to explore as more research is needed in this field.

### Conflict of interest

The authors have no conflict of interest to disclose.

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