DO WE REALLY UNDERSTAND THE DIFFERENCE BETWEEN OPTIC NERVE HYPOPLASIA AND ATROPHY?

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I. CHANGING CLINICAL PROFILE OF OPTIC NERVE HYPOPLASIA

Hypoplasia of the optic nerve is a developmental anomaly in which there is a subnormal number of axons within the affected nerve, although the mesodermal elements and glial supporting tissue of the nerve are normal.[1,2] Though once considered rare,[3,4] optic nerve hypoplasia is now appreciated to be a relatively common congenital anomaly that may present with a wide spectrum of visual disabilities.[5] Although it was once thought that this anomaly was only compatible with very poor visual acuity it is now well documented that it may occur even in the presence of normal visual acuity or subtle visual field changes.[6,7]

Optic nerve hypoplasia may occur as an isolated defect or in association with facial, ocular, or cranial anomalies.[2,5] A number of distinct endocrine developmental problems as well as central nervous system anomalies are associated with optic nerve hypoplasia. Indeed, as will be discussed later in this paper the variety and wide distribution of anomalies associated with optic nerve hypoplasia is often cited when discussing a proposed pathophysiological model for this optic nerve anomaly.[2,8,9]

The diagnosis of optic nerve hypoplasia in the extreme case is not usually difficult to make. The disc substance is markedly reduced and usually surrounded by an area of bare, exposed sclera which appears to coincide with the gap between the retinal pigment epithelial border and where a normal sized disc should have extended.[4,5] The retinal nerve fibre layer is variably thinned and the disc itself may appear grayish or even white in colour.[1,3] A diagnosis becomes much more difficult when the degree of hypoplasia is less extreme, or even segmental in nature. The diagnosis of optic nerve hypoplasia remains primarily a clinical one. Infrequently photographic evaluation of the ratio of vessel size and disc size or the discmacula to disc diameter ratio may lend assistance in establishing the diagnosis.[11] Axial tomography of the optic canals, and ultrasound evaluation of the orbital portion of the optic nerve have proven to be less useful especially in the most perplexing, subtle cases.[12,13]

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II. AETIOLOGY

No single aetiological factor has been identified in the pathogenesis of optic nerve hypoplasia.[5] Genetic factors do not appear to be important as only a few rare cases have been reported to be associated with autosomal recessive[14,15] or autosomal dominant[16] inheritance. Optic nerve hypoplasia may also be associated infrequently with trisomy-18[17] and trisomy-21.[18] Although in cattle it has been clearly documented that mothers infected with a mucosal virus are at risk of giving birth to calves with optic nerve hypoplasia,[19] the role of maternal infection in human cases of optic nerve hypoplasia remains unclear. Although it has been reported that optic nerve hypoplasia may be associated with intrauterine cytomegalovirus[20] or hepatitis[21] infections, it should be remembered that these are relatively ubiquitous infectious agents and only a well controlled population-based study would be adequate to establish an infectious aetiology in these cases.

The role of teratogens in some cases of optic nerve hypoplasia has been more convincingly established. Maternal ingestion of quinine,[22] dilantin,[23] LSD,[24,25] and PCP[26] have all been reported to be associated with optic nerve hypoplasia in infancy. However, it is in the fetal alcohol syndrome where the role of a teratogen has been most convincingly proven to be important in the genesis of optic nerve hypoplasia.[27–29] Optic nerve hypoplasia has been documented to be a common finding in the rat model of the fetal alcohol syndrome.[27] In a large study of affected human infants, Stromland reported that 48% of patients identified with the fetal alcohol syndrome had optic nerve hypoplasia.[28] She also emphasised that blood vessel tortuosity was a pronounced feature in these cases;[28] in sharp contrast to those cases unassociated with the fetal alcohol syndrome. It is perhaps noteworthy that in our experience optic nerve hypoplasia in the fetal alcohol syndrome is rarely severe and the impact on visual function is mild to moderate in severity.

III. PATHOGENESIS

It is in the area of pathogenesis where the most interesting

questions and paradoxes arise in regards to optic nerve hypoplasia, especially in contrasting it to perinatal optic nerve atrophy. For some time it was believed that optic nerve hypoplasia resulted from a primary failure in differentiation of the retinal ganglion cell layer between the 13 and 17 mm stage of embryonic growth.[1,3,6] Pathologic studies however challenge this simplistic notion.

As early as 1956, Mann challenged this notion of primary failure of ganglion cell development.[30] She studied a 27 mm anencephalic fetus with an entirely normally differentiated retina. Normal ganglion cells, amacrine and horizontal cells, abundant nerve fibres, and normal sized optic nerves were noted. In contrast, she reported that in a full-term anancephalic fetus a normal outer retina was noted but a complete absence of nerve fibres, sparse ganglion cells and optic nerves consisting of only glial and connective tissue was noted. She concluded that a secondary degeneration of retinal cell axons after central connections had been made accounted for the findings in the full term anencephalic infant.

Careful histopathological study of eyes with optic nerve hypoplasia lend weight to this secondary degenerative thesis.[17] Mosier and coworkers noted that in cases of optic nerve hypoplasia the retinal ganglion cells were reduced in number but horizontal and amacrine cells were normal in appearance and number.[17] They argued that this observation was inconsistent with the primary ganglion cell development failure thesis in optic nerve hypoplasia. They stressed that amacrine and horizontal cells come from the same stem cell precursor as retinal ganglion cells. A primary failure of this stem cell line to develop should affect just the ganglion cells but amacrine and horizontal cells as well.

In the past two decades investigators have documented an extraordinary drama within the developing visual pathways. Massive retrograde optic nerve fibre degeneration and retinal ganglion cell death occurs normally as an essential stage in the development of the visual pathways in animals.[31,32] An excessive number of ganglion cells are generated during embryogenesis; presumably, this redundancy provides for some plasticity in response to early damage to the developing systems. It appears that those cells whose axons fail to secure appropriate synaptic connections die.[33] In an elegant study of human fetuses, Provis and coworkers have identified a comparable process.[34] They found that a peak of 3.7 million axons could be identified at 16 to 17 weeks gestation followed by a very rapid decline to the normal adult number of 1.1 million axons by the 31st gestational week. Could an exaggeration of this normal developmental process account for the pathogenesis of optic nerve hypoplasia?

The precise mechanism that controls and determines the trajectories of the developing optic nerve axons has yet to be precisely defined. However it is clear that the optic stock is an essential conduit along which the axons grow. Silver and coworkers[35] have observed extracellular tunnels within the optic disc and stock that may provide directional and topographic information for outgrowing optic nerve fibres. These channels are absent in mutant mice with congenital optic nerve aplasia.[35]

Astute clinicians,[2,9] aware of the literature on the dynamics of the developing visual pathways, have begun to view optic nerve hypoplasia as more of a 'atrophic process' than developmental failure.[2] They cite the frequent and diverse central nervous system anomalies associated with optic nerve hypoplasia.[9,36] Could it be that the associated central nervous system lesions are the primary problem? That is, they interrupt the normal structural conduits and/or appropriate synaptic connections of the developing visual pathways and thus precipitate excessive axonal degeneration leading to the clinical picture of optic nerve hypoplasia. This argument becomes most compelling when two sets of patients with optic nerve hypoplasia studied by Taylor and his colleagues are examined.[8,37] In the first group,[8] optic nerve hypoplasia was identified with congenital tumours (primarily glioms and craniopharyngiomas) involving the visual pathways. How else are we to explain this association other than to conclude that the tumours already present *in utero* interfered with developing visual pathways thus producing hypoplasia of the optic nerves? Even more compelling are those patients that have a retinal dystrophy associated with 'colobomata' of the macula and an exquisitely segmental optic nerve hypoplasia comprising primarily the axons of the papillomacular bundle.[37] The correlation of the macular lesions with the segmental involvement of the papilomacular axons is so specific as to suggest that optic nerve hypoplasia may result from ascending as well as descending neuronal death.

IV. THE PROBLEMS

The evidence appears to be overwhelming against any thesis concerning optic nerve hypoplasia that invokes a primary ganglion cell developmental failure thesis. Yet, there are problems with the secondary axonal death thesis as well. (1) How do we account for the fact that both hypoplasia and atrophy may occur in the same nerves? Most cases of severe optic nerve hypoplasia are tiny white nerves in sharp contrast to most segmentally hypoplastic nerves that appear pink and otherwise healthy. Hoyt and coworkers[38] have described a unique fundus finding in some cases of congenital hemianopsia. A topographically distinct pattern of retrograde axonal degeneration may be seen in each optic nerve and retina. In addition to the obvious segmental atrophy seen in these nerves Hoyt *et al.* have emphasised that the horizontal diameters of these nerves were also reduced suggesting that they were hypoplastic as well as atrophic. It is of interest that a similar patient with a congenital hemianopsia reported by Margo and coworkers[39] was judged to have the same unique and topographically specific optic atrophy but with normal sized nerves. What accounts for the disparity in the fundus in this apparently similar clinical syndrome? (2) How can we invoke excessive prenatal axonal death to account for both optic atrophy and optic nerve hypoplasia? The simplistic answer has been that the timing of the 'insult'

determines whether atrophy or hypoplasia results.[40] This argument does not adequately explain problem number 1, but even more importantly the timing issue is suspect on its own. Most authorities agree that optic nerve hypoplasia has occurred by the tenth week of gestation.[41] Since the retina does not clearly appear until 30 days of gestation the presumed 'window of time' during which an insult to the developing visual pathways would result in optic nerve hypoplasia is 4–10 weeks of gestation. Recall however, that Provis and coworkers showed that the maximal axonal production of 3.7 million did not occur until 16 to 17 weeks of gestation.[34] This would seem to imply that insults earlier than this period of time to the developing visual pathway should be compensated for to some degree by the normal excessive axonal production which is still underway. (3) How do we account for the fact that optic nerve hypoplasia and optic nerve atrophy may occur in different patients with a similar syndrome? For example the recent study of crack cocaine babies at San Francisco General Hospital has demonstrated that some children will have optic nerve hypoplasia whereas others will have optic atrophy. Is this too just a matter of timing or are there other factors to account for the coexistence of these distinctly different optic nerve problems in the same clinical setting.

V. CONCLUSION

Optic nerve hypoplasia is now recognised as a frequent clinical disorder. The profile of this optic nerve anomaly has radically changed in the last 20 years and its diverse and subtle forms are increasingly appreciated by ophthalmologists. The simplistic notion that it results from a failure of ganglion cell development no longer seems to be tenable. It is enticing to endorse the notion that it represents an exaggeration of the normal process of axonal cell death that occurs in the developing visual pathways. However this thesis has its problems. Further investigation of the development of the normal optic nerve is necessary before we can unravel some of the puzzles that surround the pathophysiology of optic nerve hypoplasia and optic atrophy.

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