Optic disc morphology

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Semiology of periventricular leuco-malacia and its optic disc morphology

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Future studies that distinguish PVH from PVL may help to determine whether optic disc morphology reflects timing of injury

Periventricular leucomalacia is an end stage lesion that results from hypoxic-ischaemic injury to the white matter of the developing brain.[1] This condition occurs in 32% of premature infants[1] and is believed to develop between the 24th and 34th weeks of gestation.[2] Periventricular leucomalacia most commonly involves the optic radiations adjacent to the trigone of the lateral ventricle, and the anterior corticospinal fibres adjacent to the intraventricular foramen.[2] Clinically, it can produce decreased visual acuity, inferior visual field constriction, visual cognitive impairment, ocular motility disturbances, and spastic diplegia.[2 3]

The association of periventricular leucomalacia with optic nerve hypoplasia presents a complex diagnostic challenge for the ophthalmologist. In 1995, Jacobson et al recognised that periventricular leucomalacia produces a unique form of bilateral optic nerve hypoplasia characterised by an abnormally large optic cup and a thin neuroretinal rim contained within a normal sized optic disc.[4] They attributed this morphology to prenatal injury to the optic radiations, with retrograde transsynaptic degeneration of retinogeniculate axons after the scleral canals had established normal diameters.[4] The large optic cups can simulate glaucoma but the history of prematurity, normal intraocular pressure, and characteristic symmetrical inferior visual field defects all serve to distinguish periventricular leucomalacia (PVL) from glaucomatous optic atrophy.[5] Whether the pseudoglaucomatous cupping of PVL warrants classification as a segmental form of optic nerve hypoplasia or a congenital optic atrophy remains controversial.[5]

In many cases, however, PVL produces diffuse optic nerve hypoplasia with no enlargement of the central cup.[6] So if periventricular leucomalacia can eventuate in axonal loss with two distinct optic disc morphological outcomes, what is the ultimate determinant of morphology? A follow up study by Jacobson et al in this month's *BJO* (p 000) attempts to address this question. If timing of injury is the determinant, it stands to reason that early gestational injury would produce diffuse diminution in optic nerve size, while late gestational injury (after the scleral canals had established normal diameters) would reduce the neuroretinal rim area and produce large cups with normal sized discs.

This correlation would have far-reaching diagnostic implications, as the morphology of the optic disc could be used to assign an approximate timing of CNS injury. This study attempts to use neuroimaging to distinguish two types of PVL that reflect pathophysiological processes known to occur at different times in gestation. The authors use the term periventricular haemorrhage (PVH) to describe the periventricular haemorrhagic necrosis that is caused by venous infarction.[7 8] This lesion is distinguishable neuropathologically from PVL—an ischaemic, usually non-haemorrhagic, and symmetrical lesion of the periventricular white matter of the premature infant.[8] Unlike PVL, PVH results from early gestational injury and usually produces a unilateral lesion that is causally related to germinal matrix-intraventricular haemorrhage.[8] The venous infarction associated with PVH is particularly prominent anteriorly, while PVL has a predilection for the arterial border zones, particularly the posterior region near the trigone of the lateral ventricles.[8] Despite their pathophysiological differences, in vivo distinction is confounded by the fact that PVL can also be associated with secondary periventricular haemorrhage (termed haemorrhagic PVL). Consequently, some studies have used haemorrhagic periventricular leucomalacia (ischaemic arterial PVL with secondary haemorrhage) to designate periventricular haemorrhagic infarction (the anterior haemorrhagic necrosis caused by venous infarction),[8] demonstrating the diagnostic confusion that arises from these two overlapping mechanisms of prenatal white matter injury.

The absence of clear inclusion criteria leaves open the possibility that it is severity of injury rather than timing of injury that determines morphology

In the current study, the authors attempt to use the neuroimaging characteristics of periventricular leucomalacia to infer pathophysiology and thereby assign an approximate timing of injury. In their study design, they state that "by assessing the primary location of periventricular white matter (injury) one may conclude that PVH is the most likely primary lesion when white matter loss is located anteriorly while PVL is more likely the more posterior lesions are located." They reason that "PVH is more common in the immature neonate, around 24–26 weeks of gestation while PVL occurs later with a peak around 33 weeks", anatomical localisation can be used to estimate gestational age at the time of injury.

My concern with the methodology of this study is that it has the potential to confuse anterior PVL with PVH by assuming that anterior PVL is necessarily caused by haemorrhagic infarction. The authors are correct in stating that most PVL usually occurs posteriorly and that PVH usually occurs anteriorly. It is also true that PVH results from earlier gestational injury than PVL. The problem is that PVL is so much more common than PVH that most PVL around the frontal horns is seen in conjunction with posterior PVL and is not PVH.[9] In other words, while PVH leads to anterior PVL, most anterior PVL is not caused by PVH. Only when anterior PVL is shown to be due to PVH can it be used as a neuroimaging marker of early white matter injury.

So how can PVH be distinguished from non-haemorrhagic anterior PVL? PVH produces a large venous infarction that leads to liquefaction, absorption, and either focal enlargement of the lateral ventricle or overt porencephaly.[9] Only when there is ex vacuo enlargement of the lateral ventricle or porencephaly can one infer that PVH must have occurred and that the timing of injury was early in gestation. Neuroimaging in the "early injury" group would have to show unilateral ex vacuo enlargement of the lateral ventricles anteriorly for the authors to argue that these patients must have had an early injury with PVH rather than the more common PVL with anterior involvement. In their case definition, the authors do not specify how often the periventricular injury was unilateral, whether there was ex vacuo dilatation or porencephaly, or whether it occurred in conjunction with posterior injury (most likely PVL) or in isolation (most likely PVH). Furthermore, PVH does not always occur anteriorly in the distribu-

tion of the thalamostriate vein; it can also occur in the posterior part of the brain due to atrial vein thrombosis.[10] This posterior variant of PVH would then correlate with a diffuse reduction in optic nerve size (opposite to the prediction of the proposed model). As the notion that the territory of PVL predicts timing of injury has significant medicolegal implications, it should be regarded as a general correlation rather than an inviolate principle.

I suspect that the premise of this paper, that timing of injury in PVL correlates with optic disc morphology, is correct. However, the absence of clear inclusion criteria leaves open the possibility that it is severity of injury rather than timing of injury that determines morphology. If, for example, anterior PVL occurs when there is severe gestational injury to the developing brain, then a more severe injury to the optic radiations could simply produce a more severe degree of optic nerve hypoplasia.

So while optic disc morphology may well predict timing of injury, one must exercise caution in equating anterior PVL with early timing of injury. Future studies that carefully distinguish PVH from PVL may help to determine whether optic disc morphology reflects timing of injury.

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Deep sclerectomy
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Physiology and histology of deep sclerectomy

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Results from animal studies should be applied with caution to the human clinical situation

The paper by Delarive *et al* in this month's *BJO* (p 000) studies the aqueous outflow characteristics and histology of deep sclerectomy (DS)—with (DSCI) and without collagen implant—in a rabbit model. This increasingly popular surgery has the advantage of fewer postoperative complications, as it is theoretically non-penetrating.[1–3] The mechanism(s) by which DS and DSCI lower the IOP has been investigated non-invasively but not vigorously studied in an animal model with corresponding histology.

Ultrasound biomicroscopy (UBM) studies in human eyes that underwent DS or DSCI have demonstrated formation of a subscleral lake and an overlying bleb.[4 5] In half or more of the patients examined by UBM, a supraciliary hypoechoic area was identified.[4 5] As a result, it has been postulated that aqueous flowing through the trabeculo-descemetic membrane is absorbed into the subconjunctival space as well as the suprachoroidal space.

Physiological and histological support for some of these UBM findings is provided in the present study. Formation of an intrascleral canal was observed. This structure corresponds to the subscleral lake seen on UBM. The use of cationised ferritin in the perfusate demonstrated the development of new vessels around the canal, which may possibly facilitate drainage into a suprachoroidal space. In eyes with the collagen implant, spindle cells were observed lining the canal. These cells may help maintain the long term viability of the canal, as suggested by the slightly higher outflow facility (OF) in DSCI eyes versus DS eyes (not statistically significant).

The OF was significantly increased in both groups over the 9 months of study. This correlates well with clinical studies showing good long term IOP reduction.[1–3] However, in the rabbit model, IOP reduction was maintained for only 2 months. This probably reflects, in part, the fact that the rabbits had a normal baseline IOP (not elevated, as in glaucoma patients). At the normal pressures there is probably less outflow and lower OF, thus avoiding hypotony. This also correlates well with clinical findings in which hypotony is rare and the maintained IOPs tend to be slightly higher than in trabeculectomies.[1]

As always, results from animal studies should be applied with caution to the human clinical situation, particularly with respect to the rabbit model where inflammation and possibly vascular formation may be more vigorous. However, the authors should be congratulated for developing an excellent animal model of deep sclerectomy and providing physiological and histological evidence for the efficacy of this surgery. Future studies in primate eyes and cadaver specimens may further shed light on the mechanisms.

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