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The significance of periventricular leukomalacia on ophthalmic outcome

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Abstract

Aim: **Periventricular leukomalacia (PVL) is a type of cerebral white matter damage commonly arising within neonates born prematurely. This review aims to evaluate the literature relating to the long-term ophthalmic outcomes following PVL, focussing on the relationship between neuro-imaging and visual outcome.**
Methods: **A literature review was undertaken between October 2013 and January 2015. Articles were sourced using PubMed, ResearchGate and forward citation searches.**
Results: **PVL is shown to increase an individual's chance of developing ocular defects, namely cerebral visual impairment, strabismus, visual field defects and visuoperceptual anomalies. The severity and extent of PVL is directly proportional to both the chance of developing an ocular defect, and the severity of said ocular defect; however, there is not a perfect correlation and ophthalmic outcome is specific to each individual. There have also been reports of strabismus being the presenting factor, leading to an investigation which revealed the presence of PVL that had been missed during the neonatal period. Neuro-imaging has been shown to have some predictive ability, varying depending on the area of the visual pathway examined, and the aspect of visual outcome predicted.**
Conclusions: **While predictive results gathered via neuro-imaging can offer insight into visual outcome, these must be consolidated through non-radiological clinical testing. Strabismus has been documented as a presenting factor in patients with PVL. Therefore the initial presentation of a patient with PVL, where the diagnosis has been missed during the neonatal period, may be through the orthoptic department.**

Key words: Cerebral visual impairment, Magnetic resonance imaging, Periventricular leukomalacia, Strabismus, Ultrasonography, Visuoperceptual anomaly

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Introduction

Brain injury is a common consequence of preterm birth,[1,2] with periventricular leukomalacia (PVL), a type of cerebral white matter damage, being of importance to orthoptists owing to its location along the visual pathway.[3] Individuals with PVL can exhibit both ocular and non-ocular complications that vary in nature and severity depending on the extent of the damage. PVL affects 6–32% of neonates born prematurely.[4–8] Improvements in neonatal care have resulted in increased survival rates of all preterm children; however, this is accompanied by an increase in the morbidity rate, as increasing numbers of very low birth weight babies are able to survive infancy.[9] While PVL most often arises within neonates born prematurely, it may also occur within babies born at full term, either spontaneously, or following septicaemia or birth asphyxia.[10,11] Irrespective of the gestational age, the consequences of PVL can be severe, affecting a range of visual functions.

Methods

The literature included within this review was gathered through the use of PubMed and ResearchGate, then further accessed through the Medline, Science Direct, Index Medicus, and *British Medical Journal* databases. Forward citation searches were also undertaken. Typical key words used in literature searches initially included: periventricular leukomalacia, cerebral visual impairment, strabismus, visuoperceptual anomaly, magnetic resonance imaging and ultrasonography; however, additional key words were added over time. Further research was then implemented based on the results of the articles gathered in this manner.

More recent research was favoured; however, as there is not extensive literature published pertaining to PVL and visual outcome, where it was not possible to locate research conducted within the last 20 years, older literature was included. Studies which included individuals with a diagnosis of PVL were favoured over ones that did not, and studies written only in English were included, with the exception of one article written in Spanish.[4]

Diagnosis

Periventricular leukomalacia necessitates an early diagnosis owing to its frequently severe consequences. This

diagnosis must be reached via radiology, typically using cranial ultrasound, though magnetic resonance imaging (MRI) may also be performed.[12] There is a well developed and implemented PVL grading system attributed to MRI, with grades I–IV describing increasing severity of injury;[13] however, other less widely used grading systems are sometimes employed in clinical practice.[14] There are at present no formal UK guidelines endorsed by the Royal College of Paediatrics and Child Health detailing a screening or diagnostic pathway, resulting in some cases not being identified. This is supported by reports of strabismus being the presenting factor subsequently leading to a diagnosis of PVL.[15] Therefore the absence of PVL in the case history cannot rule it out as a possible aetiology.

Neuro-imaging

Research has focussed on whether an accurate visual prognosis can be attained early on in an infant's life, soon after PVL occurs, by observing the severity and location of damage to individual neurological structures.[16–18] However, there are different radiological methodologies, with pros and cons for each.

Computed tomography

Computed tomography (CT) is no longer widely used in cases of suspected PVL, following the advent of MRI. CT still holds some viability, however, when there is evidence of haemorrhage. In cases of hypoattenuation, i.e. areas of the brain which appear paler than anticipated, it is less useful, being less able than MRI to differentiate hypoattenuated tissue from normal white matter.[14]

Ultrasonography

Ultrasonography has been found to hold credibility in the diagnostic process both as a screening tool and where an MRI scan would not be appropriate, with the added advantage that as it can be performed at the patient's bedside it does not necessitate moving a potentially seriously unwell neonate from the neonatal intensive care unit (NICU).[19] It has also been found to deliver sensitive and specific results, though less so than those attained through MRI.

Cranial ultrasound is found to be much more efficient during the acute phase of PVL[20] and at identifying its higher grades (grades III and IV). For grades III and IV, its sensitivity and specificity have been found to be as high as 90% and 93%, respectively. For grades I and II, however, its sensitivity has been shown to drop to as low as 20%.[21]

Magnetic resonance imaging

At present, the preferred diagnostic and grading method is magnetic resonance imaging. MRI is regarded as the most sensitive and specific technique across all phases of PVL,[19] as high-resolution images are produced making accurate interpretation easier (Fig. 1). Despite this, MRI is not performed in cases of PVL until the neonate is in both a stable circulatory and respiratory state, if at all. In these cases, ultrasonography provides the initial radiological investigation.[12] Additionally, while MRI is the most effective method used in the diagnostic process it is not infallible, and therefore other radiological methods may be employed to consolidate its results.

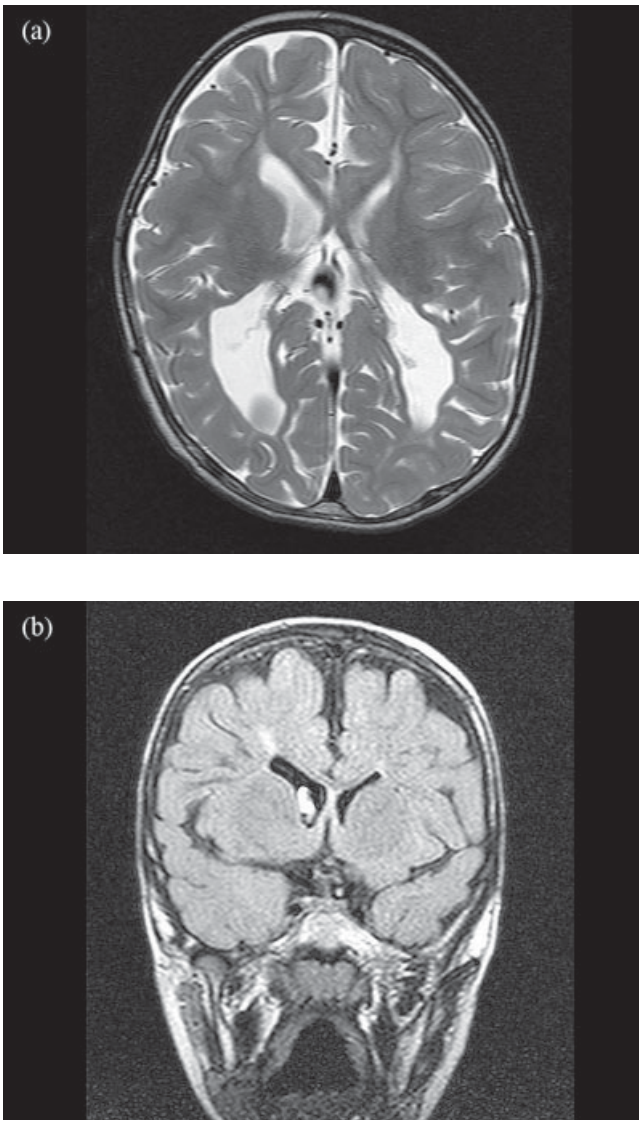

Fig. 1. Periventricular leukomalacia observed via MRI in a 2-year-old boy. (*a*) Bilaterally enlarged occipital horns are revealed, characteristic of PVL. (*b*) In the coronal plane asymmetric enlargement of the lateral ventricles can be noted, again characteristic of PVL.

Ophthalmic outcomes

The damage due to PVL is always found to be retrochiasmal,[22] with the optic radiations being most commonly affected; however, in severe cases the damage may extend into the visual cortex.[17] The wide range of resulting ophthalmic disorders include: cerebral visual impairment (CVI), strabismus, visual field defects (most often inferior),[23] nystagmus[24] and visuoperceptual anomalies.[16,19]

Non-ocular implications

In addition to the range of ocular complications, PVL

Table 1. Types of strabismus observed in children with PVL

Type of strabismus	Jacobson *et al*. (2002)[28] ($n = 48$)		Choi *et al*. (2013)[29] ($n = 60$)	
	No. of individuals	Percentage of cohort (%)	No. of individuals	Percentage of cohort (%)
Esotropia	23	47.9	17	28.3
Exotropia	14	29.2	22	36.7
Esotropic microtropia	7	14.6	0	0
Orthophoria	4	8.3	21	35.0

has been shown to be a leading cause of cerebral palsy (CP), with the extent of the CP being proportional to gestational age[25] and the presence and severity of cystic PVL.[26] Developmental delay is also a common co-morbidity,[27] and along with CP may potentially contribute to significant challenges in performing an accurate visual assessment of these children.

PVL and strabismus

Strabismus is a common finding in children with PVL but reported rates are variable, being as high as 90% in a study by Jacobson *et al*. (2002),[28] while others have reported lower values of 65%.[29] The types of strabismus observed within these studies are detailed in Table 1.

As demonstrated by the results in Table 1, strabismus following PVL can vary in type. Choi *et al*.[29] described 8 individuals with horizontal strabismus to have an additional vertical element, and there have been reported cases in which children with PVL have exhibited variable angles, even spontaneously converting from esotropia to exotropia.[19] The reduced fusional reserves frequently observed within patients with PVL are speculated to be the cause of this;[19] however, no data were found to support this theory. In addition, there appears to be no association between the anatomical site of cerebral damage and the type of resulting strabismus.[6]

This rate of strabismus is clearly higher than in the general population, recently estimated to be $<2\%$,[30] but also higher than rates reported in low birth weight (LBW) populations, which ranged from 14.4%[31] to 19.0%,[32] the highest being 20.1%[33] of LBW babies. This highlights that PVL significantly increases an infant's risk of developing strabismus, over and above the risk due to premature birth alone.

Despite the high rates of strabismus, the pathogenesis is not understood. It can be theorised that the visual disruption resulting from CVI and damage to the visual pathway may be the cause. Alternatively, the post-haemorrhagic hydrocephalus sometimes associated with PVL may be the primary aetiological factor, with strabismus potentially arising as the result of compression to the optic nerve and chiasm, disrupting the patient's developing binocular single vision.[34]

Strabismus as a presenting factor of PVL

A retrospective study by Muen *et al*.[15] reviewed 7 patients in whom strabismus had been the presenting factor, leading to a subsequent MRI investigation that revealed the presence of PVL. All patients were initially esotropic at presentation, with the average angle recorded as 29.3^{Δ} BO, and a range of $16–45^{\Delta}$ BO. Thus, all patients had substantial deviations. One patient also showed dissociated vertical deviation (DVD), pointing to a diagnosis of infantile esotropia;[35] however, the exact diagnoses of the other patients are not specified beyond this. As patients with infantile esotropia are known to exhibit angles of $\geqslant 30^{\Delta}$BO,[36] it can be presumed that patients with types of strabismus other than infantile esotropia exist within this study, based on the range of angles. In addition, all patients but one had a history of preterm birth with the average age at presentation being 2.69 years (range 7 months to 6 years). Certain patients also exhibited subtle neurological deficits, including: impaired fine motor control, speech impairment and developmental delay.[15] It was the presence of these combined factors that prompted further radiological investigation.

Impact of late diagnosis

Muen *et al*.[15] speculate that the patients' late diagnosis of PVL could have impacted upon their education and quality of life, stating that had they been diagnosed in the neonatal period, extra support in school could have been arranged for them. It can be further concluded from this that any patient, regardless of age, presenting to the Orthoptic Department with any combination of the aforementioned signs and symptoms consistent with PVL and no prior diagnosis should be considered for further investigation, owing to the potential consequences of going undiagnosed.

Outcomes of strabismus surgery

Reported surgical outcomes in patients with PVL have variable success rates. As a result, different approaches to surgical technique specific to patients with PVL have been suggested, in an attempt to attain a more favourable outcome.[19] Of the patients included in the Muen *et al*. study,[15] 5 of the 7 individuals included underwent surgery in an attempt to correct their strabismic angle, with 3 initially achieving 'cosmetically satisfactory' results of $\leqslant 10^{\Delta}$ post-operatively, although in 2 cases the angles later increased. One became a consecutive exotrope, whilst the other's esotropic angle increased. Jacobson *et al*.[19] also note variability in surgical outcome and theorise that the optimal period for operating on children with PVL differs from that of children without PVL. It is further suggested that owing to the frequent variability of the strabismic angle in children with PVL, the amount of surgical correction should be reduced.[19]

In a study by Choi and Jung (2013),[29] the overall success rate of strabismus surgery in individuals with PVL (success being given as a measurement of $\leqslant 10^{\Delta}$), was found to be 73%, when measured 6 months post-operatively (sample size: $n = 60$[29]). Considering that 'favourable' outcomes for horizontal strabismus surgery in individuals not suffering from PVL vary between 52.7% and 93%,[37–39] (sample sizes: $n = 40$[37], $n = 304$[38] and $n = 42$[39]) a 'favourable' outcome in 73%[29] of patients can be considered a positive result, and in

Table 2. Degrees of visual impairment pertaining to varying degrees of PVL

Uggetti *et al*. (1996)[18] ($n = 27$)				
PVL severity groups	Individuals with normal acuity *n* (%)	Individuals with mild impairment *n* (%)	Individuals with moderate impairment *n* (%)	Blind individuals *n* (%)
Severe	0	0	1 (25)	3 (75)
Moderate	2 (14)	1 (7)	11 (79)	0
Mild	8 (89)	1 (11)	0	0

Cioni *et al*. (1997)[17] ($n = 48$)		
PVL severity groups	No. of individuals *n* (%)	Individuals with visual impairment *n* (%)
Severe	14 (29)	8 (71)
Moderate	34 (71)	4 (12)

keeping with results following strabismus surgery in the general populace. Despite this, it is unknown what surgical techniques were employed to attain this outcome.

Visual functions

CVI is the leading cause of childhood bilateral visual loss in the UK[7,40,41] and the developed world.[42] CVI is defined as a bilateral reduction in vision in the absence of any ocular pathology, and when caused by PVL typically arises following damage at the level of the optic radiations.[17]

Visual acuity (VA) is the standard measure of determining visual function; however, CVI can occur in the presence of normal VA where the visual dysfunction takes the form of visuoperceptual anomalies.[43] Despite this, VA continues to be the most common measure of visual function reported, even in children with CVI, therefore potentially underreporting the prevalence of CVI.

Visuoperceptual deficits as the result of PVL

While strabismus and CVI resulting from PVL have been well documented, the visuoperceptual (VP) difficulties that commonly arise are less widely described. The pathogenesis of visuoperceptual anomalies is not fully understood,[16] and many different aspects of impairment have been documented to result from PVL. In addition, no reports detailing an incidence of VP anomalies in children with PVL were found.

Aspects of VP difficulties arising within individuals suffering from CVI include: simultanagnosia (difficulty perceiving more than one object at a time), prosopagnosia (difficulty with recognition of familiar faces), global motion processing deficits (difficulty surrounding visual detection of the speed and direction of a moving object) and difficulty with hand-eye co-ordination.[16,44,45] Another common finding in children showing VP difficulties is the inconsistency noted between a child's verbal ability and their measured IQ. While specific VP deficits may not be detectable on a standard orthoptic assessment, a common finding in these children is the exacerbation of the crowding effect upon acuity testing.[46]

Relationship between imaging results and visual functions

Given the high rates of ophthalmic disorders resulting from PVL it would be beneficial if the imaging results could be used to inform the creation of targeted screening guidelines. Research has been undertaken to ascertain whether an association exists between severity of PVL and the degree of resulting visual impairment, and whether VA in individuals with PVL can be predicted objectively using radiology. Both aims involve observing severity and extent of damage to areas of the visual pathway using neuro-imaging, and further comparing this with results from subjective clinical VA testing.[17,18] Specific data regarding the association between severity of PVL and severity of visual impairment, observed with Teller Acuity Cards (TAC), are given in Table 2.

Correlation between radiological and non-radiological findings

As can be seen in Table 2, more extensive PVL is associated with greater reductions in VA. Damage extending to the visual cortices is found to be a highly significant finding, indicative of a poor visual outcome.[18] Cortical damage was observed in all children classified as blind, with damage to the visual cortex appearing to always occur in the presence of damage to the optic radiations. The children with more severe damage to the optic radiations were found to be 3 times as likely to suffer from CVI as those with mild damage; however, certain children exhibiting mild/moderate optic radiation damage could be demonstrated to have normal VA.[18] Owing to this, it can be concluded that the presence of mild periventricular damage does not necessarily mean that VA will be significantly affected. This further indicates that an accurate assessment into VA can only be reached by additional non-radiological testing, especially in children with damage to the optic radiations only.

Thalamic damage was noted in 3 children with severe PVL by Uggetti *et al*. (1996)[18] and has subsequently been found to coincide with PVL in its more severe forms.[47] Damage to the thalami has been documented as

Table 3. Sensitivity and specificity of fMRI in the prediction of visual acuity

Yu *et al*. (2011)[50] ($n = 24$)			
Examination of optic radiations		Examination of visual cortex	
Sensitivity	69.3%	Sensitivity	15.4%
Specificity	82.3%	Specificity	100%
Overall accuracy	75.8%	Overall accuracy	32.7%

a cause of vertical gaze palsies;[48,49] however, no reports were found documenting vertical gaze palsies in individuals affected by PVL.

The predictive ability of MRI

The sensitivity and specificity of MRI observed by Cioni *et al*.[17] were found to differ depending upon the area of the visual pathway examined. The results are detailed in Table 3. The specificity and subsequent overall accuracy of examination of the visual cortex gives the impression that MRI cannot reliably be used to predict visual outcome, especially in cases of cortical damage. Despite this, cortical damage is only observed in the most severe grades of PVL[18] and therefore will not have been present in the majority of this cohort, accounting for the low sensitivity when predicting reduced VA. The specificity was conversely found to be 100%, suggesting that the presence of cortical damage is in fact highly indicative of a poor visual outcome, contrary to the overall accuracy shown in Table 3.

The predictive ability of fMRI

As imaging technology has progressed, the introduction of functional magnetic resonance imaging (fMRI) has provided more data to analyse the relationship between imaging findings and visual functions. Yu *et al*.[50] demonstrated a statistically significant association between fMRI findings (in terms of the active number of voxels in the visual cortex) and the results of the Teller Acuity Card (TAC) testing ($p < 0.001$). Twenty-one children with a diagnosis of PVL (age range 0.6–1.5 years) were compared with 16 age-matched controls (age range 0.5–1.5 years). The fewest active voxels in the visual cortex were observed in the children with the lowest VA observed on TAC testing. The children with PVL and seemingly unaffected VA also demonstrated fewer active voxels than their non-PVL preterm counterparts. This suggests that PVL may cause an overall reduction in cerebral white matter while sometimes not outwardly affecting VA. It is also possible that CVI may still have been present in the children with normal acuities, in the form of visuoperceptual anomalies.

Association between imaging data and visuoperceptual problems

As stated previously, visuoperceptual deficits can arise as a result of PVL. At present, there is no age-appropriate way to accurately assess these in an individual under 4 years of age. Owing to this, it can be speculated that any significant ability of neuro-imaging to predict VP anomalies could be included in a diagnostic pathway, as neuro-imaging can be performed objectively in an individual of any age. This would further the interest of pre-emptively putting measures into place to aid a child in adapting to these deficits as they develop, e.g. through the use of occupational therapy,[51] and would make this possible to achieve before the child reaches school age.

A method sometimes used to assess VP anomalies is the developmental test of visual perception (DTVP).[52] A study by Fazzi *et al*.[16] aimed to correlate data from the DTVP with MRI results in children (mean age 6.95 years) with PVL.

On MRI, 15 of 20 children (75%) were found to have reductions in their occipito-parietal and posterior-parietal white matter.[16] These fibres are known to correspond to visual perception, and have also been shown to contribute in the visual tracking of objects,[53] a skill essential in hand-eye co-ordination. The finding of parietal lobe damage on MRI was significantly correlated with the presence of visuoperceptual anomalies ($p < 0.001$).

The most significantly affected areas of visual perception noted using the DTVP were: identifying an object based on limited visual information, hand eye co-ordination, and the ability to integrate individual parts of an image.[16] Damage to the dorsal and ventral streams can be speculated to be the cause of this.

The dorsal and ventral streams

The dorsal and ventral streams are known to originate in the primary visual cortex, with the ventral stream terminating in the temporal lobe and the dorsal stream in the parietal lobe.[54] Whilst the function of each stream is not completely understood, the ventral stream is thought to aid in the discrimination and recognition of objects through visual input.[55] The dorsal stream has been thought to correspond to the co-ordination of movement based on visual input. This would include ascertaining an object's location in space, and directing a skilled movement towards it, i.e. hand-eye co-ordination.[56]

While parietal white matter damage, and thus dorsal stream damage was observed within the cohort, accounting for the deficiencies in hand-eye co-ordination, no damage to the temporal lobe and thus the ventral stream was measurable. This leaves certain aspects of the visuoperceptual deficits measured unexplained (i.e. simultanagnosia and prosopagnosia) when using neuro-imaging alone, and suggests a diminished predictive ability.

Conclusion

Periventricular leukomalacia is known to give rise to a range of ophthalmic deficits. The incidence of strabismus in these children is shown to be considerably higher than in both non-PVL LBW babies and the general populace. CVI is also a common finding, with higher grades of PVL giving rise to larger reductions in visual acuity. CVI may also occur in the presence of normal visual acuity, taking the form of visuoperceptual deficits.

Visuoperceptual deficits are also attributable to the presence of PVL, and these may occur in a range of forms.

The ability of imaging modalities to predict aspects of visual outcome in patients affected by PVL has been demonstrated to vary based on the aspect of visual impairment predicted and the radiological method in question. MRI would be the radiological method of choice; however, ultrasonography and fMRI have both been shown to be viable for investigating certain aspects of visual function. The consensus within the literature is that structural damage examined through MRI scanning can be correlated with: the presence and severity of CVI, increased risk of developing strabismus, and the presence and nature of certain visuoperceptual deficits – with varying degrees of success. Evidence also shows that visual outcome can be more accurately predicted in more severe forms of PVL.

While there is evidence stating that neuro-imaging can be effective in the identification of probable visual impairment, there is also consensus that it is not a consistent enough tool to be relied upon solely, and may only offer limited insight into an individual's long-term ophthalmic outcome. Results gained via neuro-imaging must be consolidated using the results from a non-radiological examination, highlighting the continued importance of the orthoptist's role in performing an accurate visual assessment of these patients.

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