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Ocular signs, visual and general developmental outcome in Indian children with radiologically proven periventricular leukomalacia

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Purpose: Owing to the paucity of literature on Indian children with periventricular leukomalacia (PVL), this retrospective study aimed to describe the visual and associated developmental abnormalities in a series of affected children attending a tertiary level eye care facility. **Methods:** Children with radiologically confirmed PVL who attended the Pediatric Department of a tertiary eye hospital were included and underwent a detailed ocular and general developmental assessment. **Results:** Of the 75 children, the mean age was 2.3 years, the mean follow-up was 3.1 years, 68% were males and 43% were born preterm. Grade I PVL was identified in 13 children (17%), Grade 2 PVL in 39 (52%), and Grade 3 PVL in 23 (31%). Premies with ≤2 kg (72.5%) and term babies with >2 kg (75%) had a greater association of PVL occurrence with a preponderance to severe PVL; 46% of the children were visually impaired which was significantly higher in the children with Grade 3 PVL (74%) than those with Grade 2 PVL (15%). Strabismus was common (80%) with a change in deviation over time. Seventy-one percent of the children had a refractive error, frequently myopic astigmatism. All the children except two had a delay in one or more general developmental milestones. **Conclusion:** PVL occurrence is observed both in the babies born at term and premies, resulting in significant ocular and systemic morbidities. We recommend a system in place for early identification and referral to initiate an early intervention program which goes a long way toward improving the quality of life in these children.

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The developing visual system is susceptible to hypoxic-ischemic damage both *in utero* and as a consequence of preterm birth. The impact of the injury depends on the site, severity, and extent of the damage, and the maturity of the brain at the time of insult.[1,2] Although traditionally, periventricular leukomalacia (PVL) is defined as a brain lesion caused by hypoxic-ischemic events before 34 weeks gestational age.[3] There are also case series reporting PVL in term infants.[4,5]

Neuroimaging abnormalities in children with PVL are confined to subcortical white matter, which is also called white matter damage of immaturity (WMDI).[2,3] Magnetic resonance imaging (MRI) is the most sensitive method to diagnose and grade WMDI.[3] The typical lesions of PVL involve at least the superior portion of the optic radiations, which gives rise to the inferior visual field defects. The other lesions occur in the subcortical white matter serving the visual and association cortices, which leads to both ocular and neurological manifestations.[6] The ocular and visual function abnormalities reported in PVL include refractive errors, reduced visual acuity, restricted visual fields, strabismus, optic nerve abnormalities, nystagmus, and perceptual visual impairment.[7] The neurological manifestations include cognitive impairment and developmental delay. Prompt diagnosis of the affected children will facilitate early rehabilitation with significant benefits for the child.

In India, there has been a recent rapid expansion of services for sick and preterm newborns, particularly at the district level, where more than 800 Special Newborn Care Units have been established since 2005. This is likely to increase the number of children who survive with PVL.[7] However, to our knowledge, there have been no reports on ophthalmic findings in the affected children in India.

The purpose of our study is to describe the risk factors for PVL, the range of clinical findings, and their relationship with the risk factors and severity of PVL in a series of children with radiologically confirmed PVL.

Methods

The study was approved by the institutional review board and adhered to the tenets of the Declaration of Helsinki. It was undertaken in the department of pediatric ophthalmology in a tertiary level non-government eye hospital in South India.

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The following children were included—under 10 years of age with MRI-proven PVL of any grade (all scans were interpreted and reported by the same radiologist) who were on a regular follow-up with intervention program and attended our center in the year 2014 for a follow-up visit and whose parents consented to participate. Children with clinical evidence of neurodegenerative disorders, chromosomal abnormalities or inborn errors of metabolism, retinopathy of prematurity, or other ocular disorders which could cause visual impairment were excluded.

The diagnosis and grading of PVL were established on the basis of MRI findings according to the following criteria: Grade 1 (mild): abnormally high signal intensity in the periventricular white matter on T2-weighted images, most commonly observed bilaterally in the trigone regions of the lateral ventricles; Grade 2 (moderate): loss of periventricular white matter in the regions mentioned above with abnormally high signal intensities, and ventricular enlargement; Grade 3 (severe): focal and extensive cystic changes in the white matter.[8]

After obtaining written consent from the parents, the medical records were carefully reviewed, followed by confirmation with the parents for the following details: antenatal, natal, and neonatal events; medical problems (seizures); status of visual functions; other ocular and general problems, details of any medical/surgical interventions or other treatments. Preterm birth was defined according to the World Health Organization (WHO) criteria as a live birth occurring before the start of the 37th week of pregnancy.[9] All the children underwent detailed ophthalmic evaluation by a pediatric ophthalmologist and a rehabilitationist with experience in assessing visually impaired children with and without neurological morbidities.

The ocular examination included visual acuity assessment using age- and ability-appropriate tests (LEA symbols, preferential looking, Cardiff acuity, Sheridan Gardiner, and Snellen's tests). The children who could not be tested using these methods were assessed for fixing and following, or their ability to pick up very small cake decorations (hundreds and thousands). The standard protocols were used to assess the ocular motility and strabismus, and color vision using the Ishihara pseudo-isochromatic plates where possible. The visual fields were assessed by confrontation in the children who could cooperate. The anterior segments were examined using a hand-held slit-lamp. The retinoscopy was performed after obtaining cycloplegia with homatropine 1%, followed by an estimation of the refractive error subjectively in the children who could cooperate, and objectively in the others. Finally, a detailed fundus evaluation was done by indirect ophthalmoscopy.

The visual impairment was categorized according to the WHO criteria as follows:[10] Moderate vision impairment (VI)—distance visual acuity of less than 6/18 to 6/60 in the better eye; severe vision impairment (SVI)—less than 6/60 to 3/60; and blindness (BL)—less than 3/60. As many of the children at the presentation were too young for definitive visual acuity assessment or had a neuro-developmental delay, it was difficult to distinguish SVI from blindness. A separate category of SVI/BL was created for these children.

The baseline general developmental assessment was completed with the Oregon Skill Inventory (OR Project).[11] The OR Project is a comprehensive assessment designed for use with children birth to 6 years, who are blind or visually impaired. The Skill Inventory is a criterion-referenced assessment, and enables the examiner to find out the performance level of the child, select long- and short-term objectives and execute an appropriate intervention program.

The general developmental milestones were grouped objectively as normal, mild to moderate delay, and significant delay. The children who had attained age-appropriate milestones at the last follow-up were categorized as normal. The children who had improved milestones as compared to the previous visits, however, were still not age-appropriate were considered to have mild to moderate delay. The children with no\poor improvement in the milestones/during the subsequent visits were categorized under significant delay. The above tests and categorization were done by a single rehabilitationist who was trained in handling children with vision impairment both as a single entity or in association with multiple disabilities.

Statistical analysis – The Chi-square test/Fisher's exact test for association, t-test/Mann–Whitney U test, Kruskal–Wallis, and two sample proportion tests for the comparison of the variables and percentages among the groups were used. All the analysis was done using statistical software STATA 14 (TX, USA).

Results

Study population

Among the 75 children recruited, 51 (68%) were males and 43 (57%) had been born preterm. Their mean age at the first presentation was 2.3 years (range 2 months to 8 years), and the mean follow-up was 3.1 (range 1.2–7.8) years. The mean birth weight (B. Wt) among those born preterm was 1.8 kg (range 1.2 –3.0 kg) and 2.4 kg (range 1.8–3.5 kg) among those not preterm.

PVL grades in relation to the gestational age and B. Wt

Thirteen children (17.3%) had Grade 1 PVL, 39 (52.0%) had Grade 2 and 23 (30.7%) had Grade 3. Among the 43 (57.3%) children born preterm, 16 (21.3%) had Grade 3 PVL which was not statistically different from the proportion of children born at term (7/32, 21.9%). Among the premies, with ≤2 kg as B. Wt (72.5%) and among the term babies with >2 kg as B. Wt (75%) have a greater association with PVL occurrence ($P < 0.001$.) also showing a higher preponderance to severe forms of PVL [Table 1].

Antenatal complications

In total, 29 (19 preterms, 10 terms) mothers have had complications during pregnancy. Eclampsia with or without premature rupture of membranes was the commonest (14/29, 48.3%) followed by oligohydramnios (9/29 31%) [Table 2]. In total, mothers of children with Grade 2 or 3 PVL were more likely to have had antenatal complications than children with Grade 1 PVL (79.0% vs. 46.2%, respectively) (Chi-square 5.83, $P = 0.016$).

Perinatal complications

Almost three-quarters (55/75, 73.3%) of the children had perinatal complications, 13 (17.3%) of whom had more than one [Table 2]. A history of seizures was the most common entity, affecting 54.6% of the children, among whom 17.3% had other associated complications. There were no differences by gestational age (preterm, 74.4% vs. not preterm 71.9%), or by B. Wt (≤2000 g 76.5%, >2000 g 66.7%), [Table 2].

Ocular findings

Almost half the children (46%) were visually impaired and the proportion of the children increased significantly with the increasing severity of PVL, from 15.4% in Grade 1 to 73.9% in Grade 3 (P 0.002) [Table 3]. The visual fields could not be assessed in 20 children, particularly among those with Grade 3 PVL. No defects were detected in a higher proportion

Table 1: PVL grade by birth weight and gestational age

PVL Grade	Birth weight ≤2 kg (*n*=51)				Birth weight >2.0 kg (*n*=24)				Total (*n*=75)	
	Preterm <37 weeks		Term ≥37 weeks		Preterm		Term			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Grade 1	7	13.7	3	5.9	0	0	3	12.5	13	17.3
Grade 2	16	31.4	8	15.7	4	16.7	11	45.8	39	52.0
Grade 3	14	27.4	3	5.9	2	8.3	4	16.7	23	30.7
Total	37	72.5	14	27.5	6	25.0	18	75.0	75	100
P^F	0.99				0.817					

n: Number of children, F: Fisher's exact test

Table 2. Antenatal and perinatal complications in children with Periventricular leukcomalacia, Gestational age, Birth weight and Grade

	Preterm (*n*=43)		Term (*n*=32)		≤2000 g (*n*=51)		>2000 g (*n*=24)		Grade 1 (*n*=13)		Grade 2 or 3 (*n*=62)		Total (75)	
	n	%*	*n*	%*	*n*	%*	*n*	%*	*n*	%*	*n*	%*	*n*	%
Antenatal complications														
None	24	55.8%	22	68.7%	31	60.8%	15	62.5%	7	53.8%	39	62.9%	46	61.3%
Eclampsia with or without premature rupture of membranes	11	25.6%	3	9.4%	10	19.6%	4	16.7%	2	15.4%	12	19.3%	14	18.7%
Oligohydramnios	4	9.3%	5	15.6%	7	13.7%	2	8.3%	3	23.1%	6	9.7%	9	12%
Other	4	9.3%	2	6.3%	3	5.9%	3	12.5%	1	7.7%	5	8.1%	6	8%
Total with complications	19	44.2%	10	31.3%	20	39.2%	9	37.5%	6	46.2%	23	37.1%	29	38.7%
Perinatal complications														
None	11	25.6%	9	28.1%	12	23.5%	8	33.3%	7	53.8%	13	21.0%	20	26.7%
Seizures	13	30.2%	15	46.9%	18	35.3%	10	41.7%	2	15.4%	26	41.9%	28	37.3%
Respiratory distress syndrome (RDS)	6	14.0%	3	9.4%	7	13.7%	2	8.3%	1	7.7%	8	12.9%	9	12.0%
Neonatal sepsis	3	7.0%	2	6.3%	4	7.8%	1	4.2%	1	7.7%	4	6.5%	5	6.7%
Seizures + RDS	8	18.6%	2	6.3%	8	15.7%	2	8.3%	2	15.4%	8	12.9%	10	13.3%
Seizures + neonatal sepsis	1	2.3%	0	0.0%	1	2.0%	0	0.0%	0	0.0%	1	1.6%	1	1.3%
Seizures + neonatal sepsis + RDS	1	2.3%	1	3.1%	1	2.0%	1	4.2%	0	0.0%	2	3.2%	2	2.7%
Total with complications	32	74.4%	23	71.9%	39	76.5%	16	66.7%	6	46.2%	49	79.0%	55	73.3%

Two sample proportion test

of the children with Grade 1 PVL. Among the 55 who were cooperative for field testing, 21 were detected to have inferior field defects, one with general constriction.

The refractive errors were present in 53 (70.7%) children and showed no association with the severity of PVL [Table 3]. Simple and compound myopic astigmatisms were the most common refractive errors (37/53, 70%), and hyperopia was less frequent (11/53, 21%). Overall, 59 (78.7%) children were noted to have strabismus at the last visit, 55 of whom had concomitant strabismus (33 esotropias, 22 exotropias). Two children had esotropia with hypotropia due to congenital fibrosis of the extraocular muscles, one child had an exotropia due to unilateral third nerve palsy and one had Duane's retraction syndrome. Significantly, the concomitant deviations showed both new occurrences during follow-up and a conversion of one form into another, which is discussed in details under Discussion [Fig. 1]. Among the noted optic disk anomalies, optic disk cupping associated with temporal pallor and a normal-sized disk was the most common optic nerve anomaly, affecting 69.3% of the children which was higher in the children with PVL Grades 2 and 3 than Grade 1. A further three children had optic nerve hypoplasia. Almost one-third of the children had nystagmus which was also higher in Grades 2 and 3 PVL than in Grade 1. Five children who were diagnosed to have cataracts underwent surgery for the same. Among the five, two (four eyes) were left aphakic and the remaining had intra ocular lens (IOL) implantation. Two children were found to have ptosis [Table 3].

General developmental milestones

Among the 11 children who had cerebral palsy, seven belonged to Grade 3 PVL. Mild and moderate developmental delay was a frequent finding, particularly among children with Grades 2 and 3 PVL. A delay in speech was the most frequent significant delay, particularly among the children with Grade 3 PVL [Fig. 2].

Discussion

Risk factors

There are established studies attributing the occurrence of PVL to a hypoxic-ischemic event—in the babies born on or before 34 weeks gestational age.[3] There are also case series reporting PVL in term infants.[4,5] We observed that 43% of the babies were not preterm. Interestingly, 25% of the premies and 75% among the term babies weighed >2000 g. While the birth

injury is an important pathogenic factor, it is also believed that most PVL originates before birth.[4] The antenatal risk factors included intrauterine infection, premature rupture of membranes (PROM), maternal chorioamnionitis, and hypotension with impaired autoregulation.[12] In our series, eclampsia with or without PROM was noted to be a common antenatal risk factor (48.3%), particularly in the mothers of children with Grades 2 and 3 PVL rather than Grade 1. This finding correlates well with Resch B *et al*.[13] who reported a high prevalence of premature rupture of the membranes and chorioamnionitis in their series. Adverse perinatal events that correlate with the development of PVL include perinatal asphyxia, recurrent apnea, septicemia, hypocarbia, and prolonged mechanical ventilation.[2,4,9] Hatzidaki, *et al*.[8] reported that neonates with PVL suffered more frequently from respiratory distress syndrome (RDS), seizures, sepsis, requiring more days of both mechanical ventilation and oxygen administration. Our observations correlate well with the above. In total, 28% suffered from RDS either as a single entity or in association with seizures and sepsis requiring oxygen supplementation. The seizures were present in 54.6% either as a lone entity (37.3%) or in association with other complications (17.3%) Among the 54 (72%) children who required oxygen administration, 37/75 needed mechanical ventilation for an average of 4.3 (SD 3.58, range 1–15) days.

These findings suggest that PVL occurs more frequently in a situation where either or both ante and perinatal complications were prevalent. Resch *et al*.[13] noted a similar association and suggested that PVL can possibly be prevented by improved antenatal and perinatal care. All the above factors signify that the pathophysiology of PVL in these two (premies + term) sets of babies -need more detailed research in our region and a system in place toward preventing the occurrence of the said complications.

Ocular morbidities

The PVL-affected children develop various ocular morbidities like poor visual acuity, delay in visual functions, field defects, disk abnormalities, strabismus, and nystagmus.[14,15]

Impact on visual functions

During the last follow-up, 46.1% remained to be under the WHO category of vision impairment. However, among the

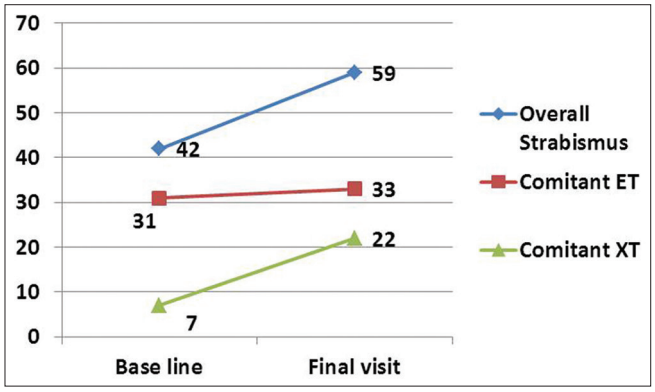

Figure 1: Change in the pattern of strabismus over time from the baseline to the final visit

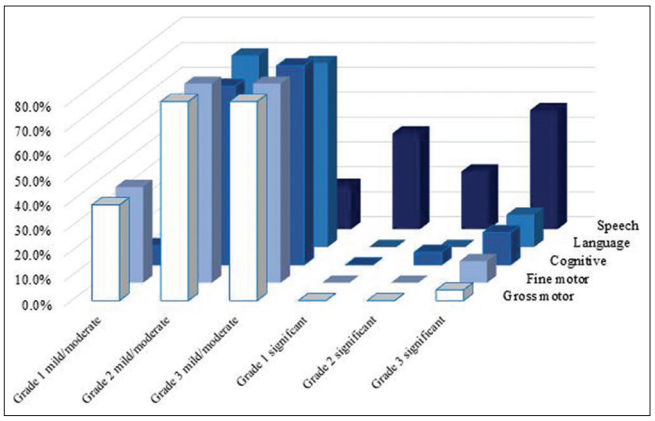

Figure 2: Developmental milestones in children with periventricular leukomalacia by grade

Table 3: Ocular findings in children with periventricular leukomalacia, by grade

Ocular signs	Grade 1 (13)		Grade 2 (39)		Grade 3 (23)		Total (75)		*P*[f]
	n	%	*n*	%	*n*	%	*n*	%	
Visual impairment									
Visual impairment	2	15.4	15	39.5	17	73.9	34	46.0	0.002
No visual impairment	11	84.6	23	60.5	6	26.1	40	54.1	
Visual Fields									
Defect detected	5	38.5	12	30.8	5	21.7	22	29.3	
Not cooperative	2	15.4	8	20.5	10	43.5	20	26.7	0.315
No defect	6	46.2	19	48.7	8	34.8	33	44.0	
Other									
Refractive error (any)	9	69.2	29	74.4	15	65.2	53	70.7	
Strabismus	10	76.9	34	87.2	15	65.2	59	78.7	
Optic disk pallor/cupping	6	46.2	30	76.9	16	69.6	52	69.3	
Hypoplastic optic disk	1	7.7	2	5.1	0	0	3	4.0	
Nystagmus	2	15.4	10	25.6	11	47.8	23	30.7	
Cataract	0	0	0	0	5	21.7	5	6.7	
Ptosis	0	0	2	5.1	0	0	2	2.7	0.145

[f]Fishers exact, *n*: Number of children

49/75 children grouped under SVI/blindness at presentation, a majority showed improvement in vision on follow-up visits except nine belonging to Grade 3 PVL, who also had a significant delay in the general developmental milestones. Though the literature supports the fact that these children show spontaneous recovery to a certain extent, we attribute the good recovery in our patients to the vision intervention program which was instituted from day 1 of the diagnosis with good compliance as evidenced by a long-time follow-up.

Refractive Errors: Contrary to Jacobson *et al*.[16] who reported that the children with PVL more commonly had hypermetropia often in combination with astigmatism, our study revealed simple and compound myopic astigmatisms as the most common refractive errors (70%), and hyperopia was less frequent (21%). This finding might be related to the higher age at the last follow-up visit.

Strabismus and nystagmus

Muen *et al*.[17] had reported PVL as an unsuspected finding in their series of strabismus. Brodsky *et al*.[7] in their series of 22 patients, reported that 12 had (XT) exotropia (55%); 8 had (ET) esotropia (36%), only 2 had no strabismus (9%). We noticed that 78.7% of the children had some form of strabismus. Among the 55 children who were diagnosed to have concomitant strabismus, esotropia was more predominant—62% than exotropia (48%). As observed by Jacobson and colleagues[18] that ET can spontaneously convert to XT in some children with PVL, we also noticed a similar phenomenon in our series. Among the 31 children with esotropia at the baseline, at the last follow-up visit, five had become exotropic, and in a further five, the deviation reduced to a minimal or no deviation. There were 12 new occurrences of esotropia during the follow-up. Among the 22 children with exotropia at the last visit, five were esotropic at the baseline; 10 remained as it is and 7 were new occurrences [Fig. 1].

Holman and Merritt[19] reported poorer results for esotropia surgery in the patients who had associated neurological conditions (55.2% satisfactory outcome), when compared with controls with 83.3% satisfactory outcome. Muen *et al*.[17] reported that only three of the seven patients in his series achieved a satisfactory outcome with strabismus surgery. From our series among the 10 children who underwent surgery for esotropia, 8 had a good outcome. One developed a consecutive exotropia, another exhibited a change in the pattern deviation from A to V. Among the three children who underwent surgery for exotropia, two had good alignment and one developed a consecutive esotropia. Overall, we had a success rate of 76.9% which could be attributed to both the type of deviation and the conservatism maintained in the surgical decision. Though our numbers are small for comparison, these findings certainly argue for a conservative and cautious approach to managing strabismus in the patients with PVL. We recommend that surgery should be considered only after a stable misalignment is confirmed on consecutive examinations. We observed almost one-third of the patients having nystagmus mostly in association with strabismus. It has been reported that a higher percentage of patients have nystagmus when tested by the eye movement recording,[20] which was not carried out for our patients.

Optic disk anomalies- Jacobson *et al*. have noted that children with optic nerve hypoplasia (ONH) and PVL can have large optic cups with normal-sized optic disks suggesting that trans synaptic degeneration of optic axons occurred late in gestation after a normal-sized scleral canal had formed.[16] Our finding of 69.3% of the children having a normal-sized optic disk, with temporal pallor and large cupping correlates well with the above observations.

General developmental milestones

It is said that between 72 and 90% of all the children with spastic diplegia have PVL, however, all children with PVL do not always develop cerebral palsy (CP). Miller SP *et al*.[5] have observed a spectrum of neurologic abnormalities, particularly, developmental delay and heterogeneous motor findings not limited to the classic spastic CP in term children with PVL. Imamura *et al*.,[21] in Japan, reported that Grades 3 and 2 PVL exhibited more severe developmental delay [Fig. 2].

In our series, a delay in the speech was observed to be a more common finding followed by language, cognitive functions, and gross and fine motor delay. Overall, children with Grade 3 PVL were more likely to have a significant delay in all the domains than the children with Grades 2 and 1. Almost all the children except two (Grade 1) demonstrated a delay at least in one domain. There was no association between developmental delay and preterm birth or no preterm birth. Overall, 62 (82.7%) required physical therapy, 43 (58.6%) required speech therapy, and 27 (36%) required long-term seizure medication.

Conclusion

With better neonatal care and increased survival rate of sick children, the region needs proper follow-up strategies for all sick infants (premature and term), to detect the visual and developmental challenges early in life to allow for proper interventions with a multidisciplinary approach, including vision rehabilitation. Elaborate research on the risk factors and development of guidelines is required to reduce the occurrence of multisystemic disease. Preventive measures like a regular follow-up of all neonates discharged from the neonatal intensive care unit (NICU) will help in the early detection of the deviation in their milestones development, and when detected, measures taken for an early referral will reduce the impact of the disease, thereby, allowing early rehabilitation. For ophthalmologists, when children present with any form of visual difficulties, accompanied by abnormal cupping or smallness of the optic disk, variable angle of deviations, with or without a delay in developing the general milestones, it is worth ordering for an MRI, as PVL has a better prognosis than the diffuse brain injury. This will also help in the referral fora multidisciplinary approach.

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Conflicts of interest

There are no conflicts of interest.

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