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MAJOR REVIEW

Periventricular Leukomalacia: An Important Cause of Visual and Ocular Motility Dysfunction in Children

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Abstract. The immature visual system in infants born preterm is vulnerable to adverse events during the perinatal period. Periventricular leukomalacia affecting the optic radiation has now become the principal cause of visual impairment and dysfunction in children born prematurely. Visual dysfunction is characterized by delayed visual maturation, subnormal visual acuity, crowding, visual field defects, and visual perceptual-cognitive problems. Magnetic resonance imaging is the method of choice for diagnosing this brain lesion, which is associated with optic disk abnormalities, strabismus, nystagmus, and deficient visually guided eye movements. Children with periventricular leukomalacia may present to the ophthalmologist within a clinical spectrum from severe cerebral visual impairment in combination with cerebral palsy and mental retardation to only early-onset esotropia, normal intellectual level, and no cerebral palsy. Optimal educational and habilitational strategies need to be developed to meet the needs of this group of visually impaired children. (**Surv Ophthalmol 45**:1–13, 2000.

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The eye and the developing visual system are susceptible to hypoxic ischemic damage both in utero and as a sequel to premature birth. In many countries the incidence of sight-threatening retinopathy of prematurity (ROP) is decreasing because of improved perinatal surveillance and cryotherapy or laser treatment,[44,70] but periventricular leukomalacia has become a major cause of visual impairment in prematurely born children.[44] Periventricular leukomalacia is a condition in which hypoxic ischemic damage of periventricular white matter results in a wide range of clinical manifestations.

Periventricular brain damage is associated with spastic diplegia,[49,51,92] mental retardation,[26,51] visual impairment with subnormal visual acuity, restriction of visual fields, and eye motility disorders.[19,41,88] The visual problems are accompanied by difficulties in visuospatial analysis and disorders of other higher visual functions of recognition, simultaneous perception, and visual memory.[41,49,65] Early diagnosis of such children facilitates implementation of habilitation programs with significant benefits for the child.[76]

I. Pathogenesis of Early Acquired White Matter Lesions

The pattern of cerebral injury found in newborn infants depends on the maturity of the brain at the time of insult. Damage to the immature brain at 24–34 weeks of gestation, either prenatally or (in prematurely born infants) perinatally, primarily affects the periventricular region. Ischemic and hemorrhagic lesions commonly occur in prematurely born in-

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fants. These lesions are frequently bilateral, with a fairly symmetrical distribution.

A. PERIVENTRICULAR LEUKOMALACIA

A combination of reduced systemic blood pressure and impaired vascular autoregulation of cerebral circulation is thought to lead to decreased perfusion of the brain in the premature infant. Reduced cerebral perfusion contributes to defective tissue oxygenation, resulting in hypoxic-ischemic brain injury. Prior to 34 weeks of gestation, the blood supply to periventricular white matter comprises an internal vasculature, which is progressively exchanged for the adult vascular supply pattern. This gives rise to a "watershed" vascular supply pattern, which is susceptible to hypoxic ischemic damage, [78] particularly posteriorly, close to the trigone of the lateral ventricles and less commonly anteriorly, adjacent to the frontal horns.

Banker and Larroche (1962) first described the neuropathological findings in periventricular leukomalacia.[1] They found small foci of necrosis, which interrupt the axons of the periventricular tracts and which may affect the corticospinal tracts and the optic radiation.

Actively differentiating and proliferating oligodendrocyte precursors are at greatest risk when white matter is immature before myelin sheath formation is complete. The timing of the development of periventricular leukomalacia suggests that these cells are particularly susceptible to ischemic damage.[48] Glutamate toxicity, free radical injury and macrophage-mediated cytokine damage have all been implicated in the pathogenesis, with developmental lack of antioxidant enzymes, probably predisposing to susceptibility. It has been speculated that free radical scavenging agents could prevent damage in an at-risk infant.

Nakamura et al performed post-mortem and angiographic studies of deep white matter in neonates with periventricular leukomalacia, which revealed changes suggestive of an alternative pathogenesis.[61] They suggested that impaired circulation in the group of deep drainage veins in the periventricular white matter leads to edema with additional venous hemorrhage in some cases. They speculate that this compromises arteriolar function and leads to coagulation necrosis in the deep white matter. Concomitant intraventricular hemorrhage leading to secondary hydrocephalus and periventricular hemorrhagic infarction superimposes additional injury.[15]

Obstetric risk factors for periventricular leukomalacia among preterm infants include hemorrhage during the first trimester, maternal urinary tract infections, neonatal acidosis at birth, and meconium-stained amniotic fluid.[77] Premature rupture of membranes, particularly in association with chorioamnionitis, is a further predisposing factor.[90] In infants who do not survive, there is widespread axonal damage in the deep intermediate white matter accompanied by glial activation associated with cytokine production.[10]

B. INTRAVENTRICULAR HEMORRHAGE, PERIVENTRICULAR HEMORRHAGIC INFARCTION

Preterm neonates with respiratory distress have a limited ability to autoregulate the cerebral blood flow. Thus, perfusion of the brain is dependent on the systemic blood pressure. An abrupt increase in the arterial blood pressure increases cerebral blood flow and plays an important role in the development of intraventricular hemorrhage. Approximately 15% of all children with intraventricular hemorrhage also show parenchymal pathology, such as a periventricular white matter lesion.[92] Such hemorrhagic infarctions may be difficult to distinguish from periventricular leukomalacia with secondary hemorrhage. Periventricular hemorrhagic infarction is almost invariably unilateral or markedly asymmetrical, and probably reflects disturbance on the venous side of the circulation. Periventricular white matter injury may be involved in the pathogenesis of but also a result of intraventricular hemorrhage.[92]

C. END-STAGE WHITE-MATTER LESIONS

When a child is examined with cerebral imaging later in infancy or childhood, the periventricular white matter pathology may be visualized. However, at that time it may not be possible to know whether periventricular leukomalacia, or hemorrhage, or both caused it. The end-stage lesion is, however, commonly described by neuroradiologists as periventricular leukomalacia.

II. Cerebral Imaging Findings

Examination of the infant brain by ultrasound can be performed in the incubator, rendering this imaging modality the method of choice in the immature neonate. Although ultrasound detects intraventricular hemorrhage, germinal layer hemorrhage, hemorrhagic parenchymal infarction, and cystic changes, its sensitivity and specificity in detecting diffuse or subtle brain injury is poor.[7,52,62,66] When extensive cystic leukomalacia is identified, however, it is highly predictive of cerebral visual impairment.[18,20]

Later during infancy and childhood, examination with computed tomography (CT) or magnetic resonance imaging (MRI) can detect permanent periventricular white-matter lesions. The findings in periventricular leukomalacia include atrophic dilatation of the lateral ventricles and a reduced amount of periventricular white matter, often around the occipital horns and adjacent to the trigone (Figs. 1 and 2). On MRI, the remaining white matter may have an abnormally increased signal on T2-weighted image, indicating permanent gliosis (Figs. 2 and 3).[28,29] In clinical practice, MRI is the most sensitive imaging modality available. Thinning of the corpus

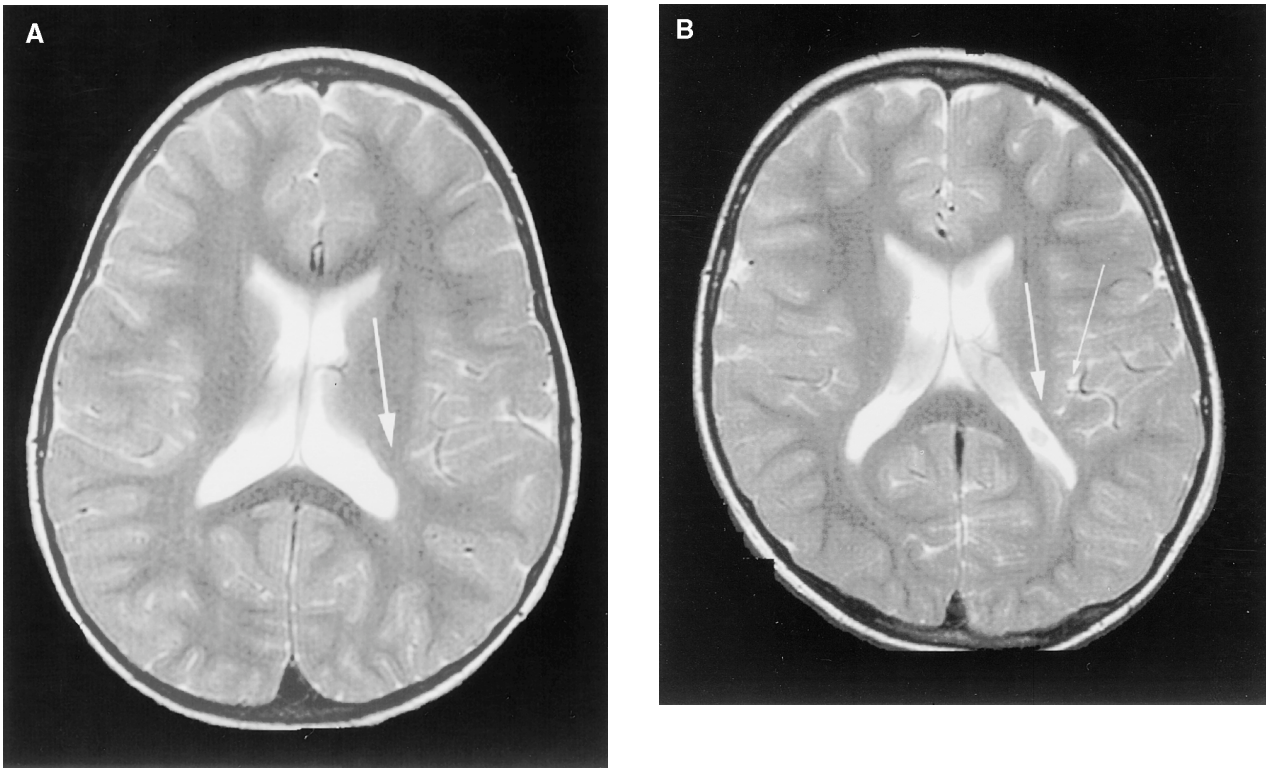

Fig. 1. A: This MR image, taken from a 4 1/2-year-old girl with a posterior fossa primary brain tumor, shows the normal amount of periventricular white matter (arrow) that should be expected in a child of this age (T2-weighted image). *B:* This is the MRI of a 5-year-old girl born prematurely, who had mild spastic diplegia with slight right-sided dominance. Note the reduced amount of periventricular white matter seen bilaterally but most pronounced on the left side (thick arrow). Also note dilatation of the deep portions of left Sylvian fissure (thin arrow). This finding is consistent with mild PVL (T2-weighted image). (Courtesy of Dr. Olof Flodmark.)

callosum and cerebellar atrophy have been found in addition to periventricular leukomalacia and have been associated with mental retardation.[52]

The severity of the MRI findings is related to the visual outcome. The more severe the periventricular leukomalacia in the peritrigonal white matter and the greater the extent of calcarine atrophy, the lower the grating visual acuity in infants and young children.[6,52,54,84] Severe cystic periventricular leukomalacia is more likely to cause reduced visual acuity and visual field impairment than moderate changes.[8,18] However, in MRI studies of the prevalence of periventricular white matter damage in prematurely born infants[58] and in ex-preterm children,[64] neither visual function nor eye alignment, fixation, or eye motility have been studied. Thus, the spectrum of visual disturbance in the mildest forms of periventricular leukomalacia remains to be determined.

III. Epidemiology

The reported incidence of periventricular leukomalacia as determined with ultrasound in the neonatal period varies from 16 to 26%.[23,73,79] In 1997, Olsén et al published a population-based study from Finland, in which MRI verified the presence of periventricular leukomalacia in 32% of all children with a birth weight less than 1750 grams, but in none of the controls.[64] Cerebral palsy was found in 9% of the study group. Visuospatial problems on neuropsychological testing was found in 60% of the preterm children and the finding of periventricular leukomalacia correlated with these problems.[65] Assessment of vision was not performed in that study.

Recently Maalouf et al showed that repeated MR images obtained in the neonatal period in infants with a gestational age less than 30 weeks revealed abnormalities of white matter in the majority of cases.[58]

Few population-based studies on the incidence of periventricular leukomalacia are, unfortunately, reported in the literature. However, periventricular leukomalacia has been identified as a common cause of cerebral palsy. MRI studies from Germany of children with spastic diplegia have shown a high prevalence of periventricular leukomalacia, especially in preterm-born children (87%).[51] Each year in the United States, approximately 50,000 infants are born with a birth weight less than 1500 grams. About 85% survive, of whom 5–15% manifest spastic diplegia

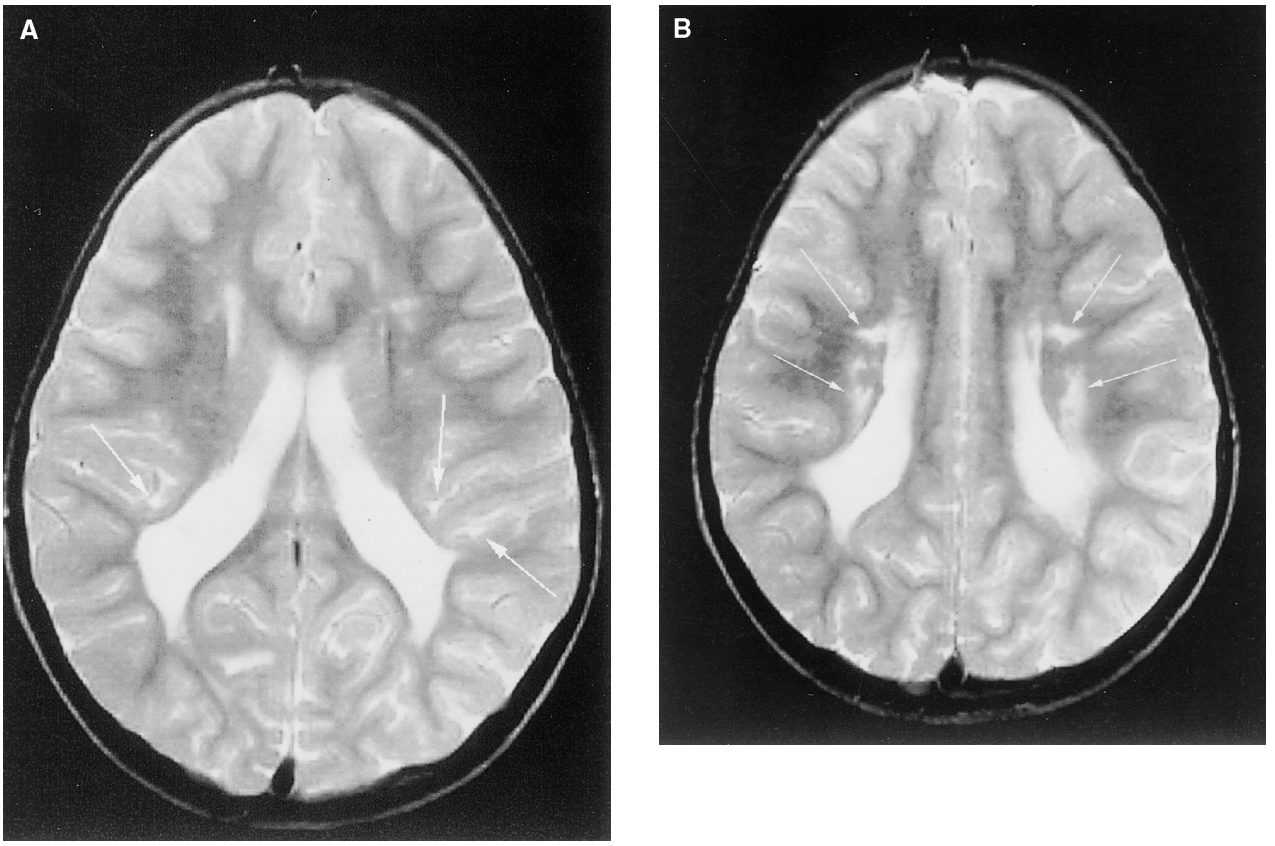

Fig. 2. This MRI is from a 4 1/2-year-old girl who was born at gestational age of 33 weeks and had visual impairment but no spastic diplegia. (T2-weighted images). *A:* Note irregular dilatation of the posterior aspects of the lateral ventricles caused by almost complete loss of periventricular white matter. Cortex deep in the Sylvian fissure about directly onto the ventricular wall. Also note the dilatation of the deep portion of the Sylvian fissures bilaterally (arrows). *B:* Note in this image, obtained further cranially than A, that the abnormally increased signal in remaining white matter in centrum semiovale (arrows).These findings are consistent with moderate PVL located primarily posteriorly. (Courtesy of Dr Olof Flodmark.)

and an additional 25–50% exhibit developmental difficulties, particularly in the context of schooling.[91]

In a recent study on a population-based group of visually impaired children born between 1989 and 1995 in Sweden, periventricular leukomalacia was found to be the cause of visual deficit in 27% of all visually impaired children and in 60% of those with a preterm birth (Grönqvists, personal communication).[44] No child in this group was visually impaired by retinopathy of prematurity.

IV. Periventricular Leukomalacia and Cerebral Palsy

Cerebral palsy, or more specifically, spastic diplegia, is a well-known clinical sequel to periventricular leukomalacia, as this brain lesion interrupts the corticospinal tracts and the manifest functional deficit has caught the attention of pediatric neurologists (Fig. 1B).[56,80,93] Between 72 and 90% of all children with spastic diplegia have periventricular leukomalacia.[37,51,63]

However, children with periventricular leukomalacia may escape cerebral palsy and exhibit only minor motor impairment, despite radiologically obvious pathology[52] and even extensive loss of brain tissue in some cases, as demonstrated by neuroimaging.[41] Olsén et al showed that 9% of a population-based group of prematurely born children had cerebral palsy, whereas 32% had periventricular leukomalacia demonstrated with MRI.[64]

V. Periventricular Leukomalacia and Mental Retardation

It has been demonstrated that preterm children without mental retardation and with normal MRI or with mild periventricular leukomalacia tend to have lower IQs than full-term controls.[52,65] Children with mental retardation (IQ $<$ 70) in association with periventricular leukomalacia have bilateral extensive white matter reduction.[52] Unilateral lesions can largely be compensated for with respect to cognitive function,[86] and mild bilateral periventricular lesions are not associated with mental retardation. Many children with spastic diplegia have reading and writ-

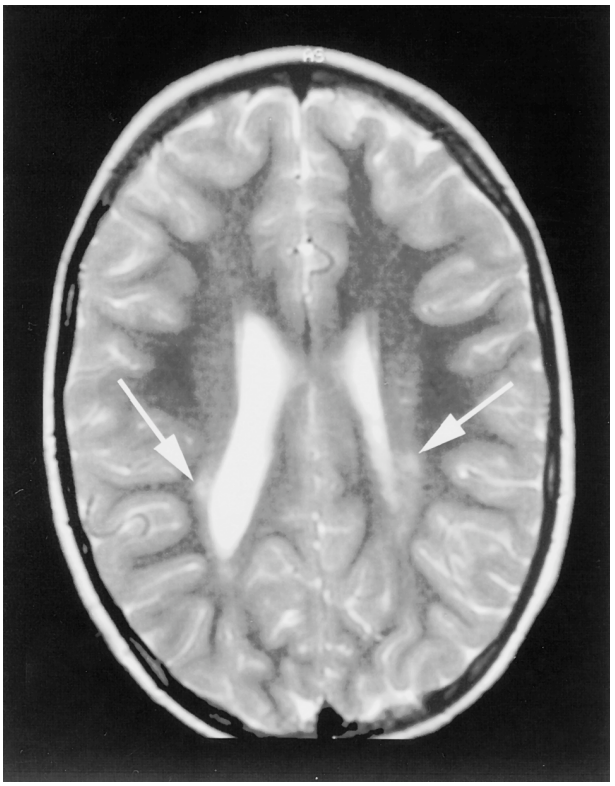

Fig. 3. This MRI (T-weighted image) is from a 5-year-old girl, born at gestational age 32 weeks, with an uneventful neonatal period, who presented to the pediatric ophthalmologist with early-onset esotropia. At 5 years she had bilateral crowding and a visual acuity with linear optotypes of 20/60 RE, 20/40 LE. Her intellectual development was normal and she did not have cerebral palsy. Note in this image through centrum semiovale subtle evidence of abnormally increased signal in white matter indicating gliosis (arrows). These findings are consistent with very mild PVL. (Courtesy of Dr. Olof Flodmark.)

ing difficulties, even if they have fairly good speech, verbal comprehension, and hand manipulation.[49]

Children with periventricular leukomalacia associated with visual impairment[41] or with cerebral palsy[24] with an intellectual level within the normal range, often have an uneven cognitive profile, with a better verbal IQ than performance IQ.

VI. Visual Dysfunction

In 1962, Banker and Larroche, who described the pathology of periventricular leukomalacia, suggested that the lesion could be expected to affect visual function, particularly the visual fields, as the axons in the optic radiation were interrupted.[1] Several investigators in the 1970s found an association between infantile encephalopathy, cerebral palsy, strabismus, and cortical defects of sight.[2,14,22,69,94] Visual evoked potentials have been employed to assess visual function in children with periventricular leukomalacia, but unlike the findings in term infants who sustain asphyxia, findings in the preterm population were not found to be predictive of abnormal outcome.[21]

A. VISUAL ACUITY

Preterm children with abnormal cranial ultrasound results that indicate periventricular leukomalacia have been shown to have reduced grating acuity.[12,18,88] Jan and Groenveld described crowding (an inability to resolve linear optotypes, while single optotypes of the same size may be identified) in children with cortical visual impairment of various etiologies.[46] Pike et al reported measurements of optotype acuity in a group of prematurely born children with different kinds of cerebral lesions.[68] They pointed out that these children often manifested visual crowding. This finding has been confirmed in children with visual impairment caused by periventricular leukomalacia.[41] In this latter study, a few children exhibited a grating acuity within the normal range when it was tested in infancy, but later developed an optotype acuity below 20/60. Thus, if grating acuity alone, or single optotype acuity alone, are tested, there is a risk of overestimating visual function.

In children with milder forms of periventricular leukomalacia, subnormal optotype acuity commonly improves gradually over the years. Children with visual dysfunction caused by periventricular leukomalacia may present with optotype acuity at any level. In some children with severe pathology, a total or near total inability to interpret optotypes may be found, although the child may well distinguish letters by sound.[45] Visual crowding is more pronounced at near than at distance.

B. VISUAL FIELDS

Restriction of the visual fields has been described both in infants with very low birth weight and as a sequel to perinatal hypoxia.[34,35,57,87] When retested two years later, the visual fields may show partial recovery in infants with perinatal hypoxia, representing a form of a delayed visual maturation.[35,87] In many cases, both hemifields are affected (bilateral lesions) and the defect is often more pronounced in the inferior field.[41, 42] Visual fields assessed with confrontation techniques tend to be more restricted than when mapped out with Goldmann perimetry in the same child. On a neuropathological basis it seems likely that restriction of the visual fields is caused by interruption of the axons in the optic radiation.[1] Variable restriction of the visual fields may also be attributable to problems with simultaneous attention.[16] Thus, the functional visual field may vary depending on the amount of visual stimuli present and on the degree of attention paid to the fixation target. In everyday situations, this phenomenon may explain problems in crowded situations, such as in traffic. It may also affect reading.

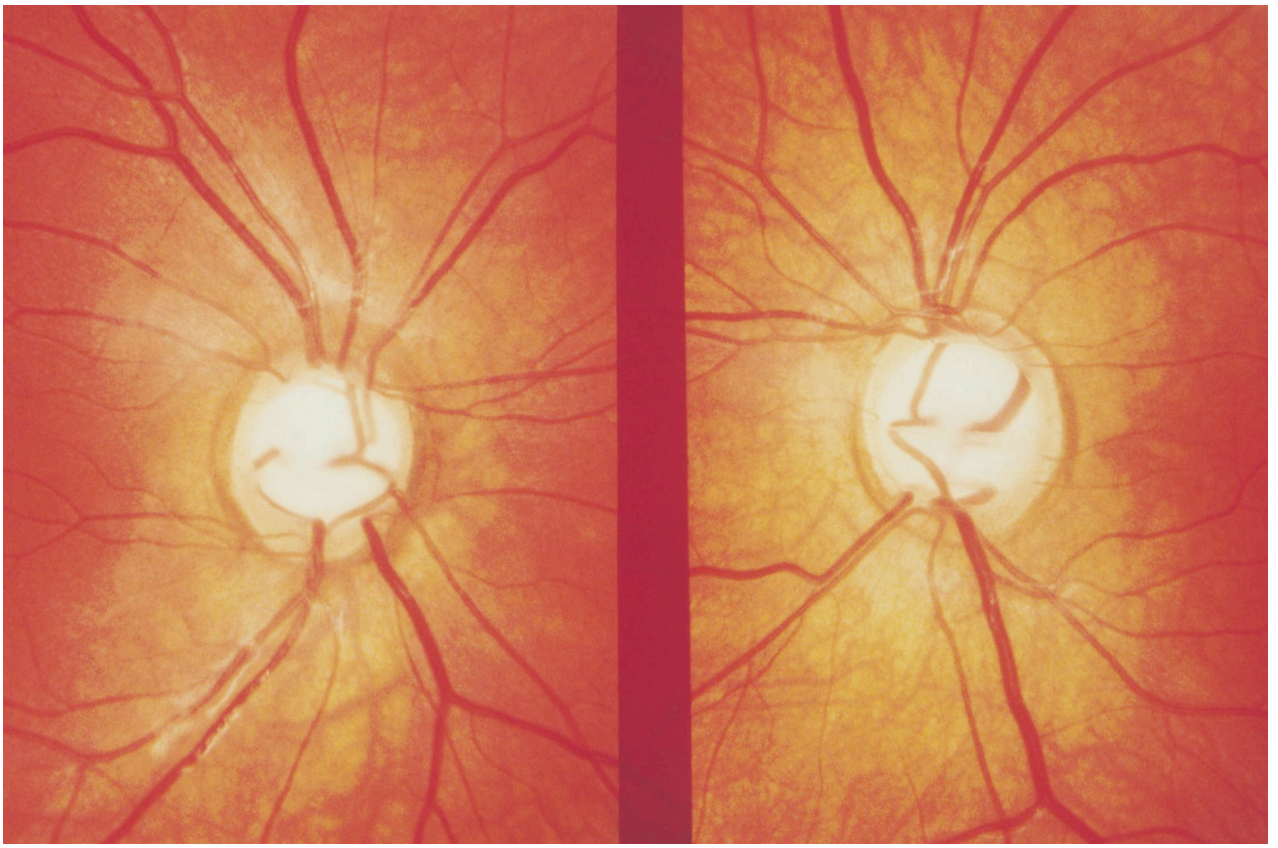

Fig. 4. Fundus photographs of an 11-year-old girl, born at term, with near normal visual acuity and a mild inferior restriction of the visual fields. Repeated measurements of IOP were normal. MRI showed a mild posterior PVL of prenatal origin. The photos demonstrate a large cup measuring 1.68 mm^2 (90% reference interval 0–1.04 mm^2) in a normal-sized optic disc measuring 2.74 mm^2 (90% reference interval 2.01–3.50 mm^2), analyzed by a specific digital image analysis technique (Hellström A).

C. COLOR VISION

Defective color vision has been described in lesions of the posterior visual system acquired in adulthood.[97] In periventricular leukomalacia, the lesion is acquired at an immature state while the visual system is still developing. The finding of near normal or normal color vision in children with visual impairment due to periventricular leukomalacia[41] may reflect plasticity during this period.

D. COGNITIVE VISUAL DYSFUNCTION

In cerebral visual impairment caused by periventricular leukomalacia, the lesion of the afferent pathway, the optic radiation, affects input of visual information and restricts visual function.[1] This visual functional deficit is further complicated by an impaired ability to process visual information, i.e., a visual cognitive disorder.[25,41,49,64,68] Children with periventricular leukomalacia perform particularly poorly in tasks requiring spatial and visuoperceptual abilities.[25,65,74] Unfortunately, there is no test battery yet designed to accurately assess these visuospatial problems in visually impaired children. It is, however, possible for a psychologist experienced in assessing visually impaired children to estimate the abilities and disabilities of a child with periventricular leukomalacia, using such standard neuropsychological tests as Griffiths, WPPSI, WISC, and NEPSY, if the child can communicate verbally.[41,49] Difficulties in processing multiple targets associated with problems making elective saccades to peripheral locations[43] are probably the principal factors responsible for such visual perceptual impairment. This may be related to pathology in the peritrigonal area involving the dorsal stream, which is the connecting pathway between striate and parietal cortices.[60]

Visuospatial constructional dyspraxia is common, particularly in children with diplegia,[50] and has not been found to be directly related to acuity, eye position, or stereo acuity. It would, therefore, appear that problems with simultaneous perception associated with a disability to make accurately directed saccades or to reach accurately in space are common. MRI studies have shown that thinning of the parietal and/or occipital white matter is manifest in children with visuospatial cognitive deficits,[33] while gliosis in the central occipital white matter is associated with impaired

hand–eye coordination and balance function.[74] Dysfunction of these pathways subserving saccadic eye movements may limit the utility of preferential looking techniques in evaluating visual function in some cases.[33]

The deficits in simultaneous perception and difficulties in making saccades to eccentric targets associated with impaired accurate reaching are very similar to those described in Balint's syndrome[36] in adults in whom bilateral occipito-parietal damage is accompanied by apraxia of gaze and impairment of simultaneous perception.

Children with periventricular leukomalacia, even those with relatively well-developed optotype acuity, may show difficulties of various degrees of severity in simultaneous perception, depth perception, recognizing familiar faces, movement perception, and in orientation.[16] Orientation problems include difficulty in navigation, both in familiar and new environments, and difficulty in finding things around the home. The reasons that white matter damage should give rise to such dysfunction is unknown, but perhaps it is related to the existence of fewer interconnections between separate cortical territories. The intellectual profiles when tested with WISC or WPPSI-R may be uneven, with higher scores on verbal than on visuospatial subtests.[41] Many children have good verbal memory, but some have problems maintaining attention. Children who have an uneven intellectual profile, with higher scores on the verbal and logical tests and a good memory, develop a battery of compensatory strategies. Recognition with the help of color is one widely used strategy. Others include recognizing people by listening to the voice or the sound of footsteps, finding things by memorizing their location and identifying objects by touch—strategies also used by totally blind children. In the school setting, such children have to constantly employ strategies to handle learning situations, and this can be exhausting.

The majority of early studies on visual function have employed ultrasound-detected lesions in the neonatal period as the inclusion criterion. Therefore, we lack information about impaired visual function associated with the milder forms of periventricular leukomalacia, which may escape detection with ultrasound.[23,62,64,73] These mild forms may represent as many as half of all children with the end stage lesions as documented with MRI. In the assessment of children with mild forms of periventricular leukomalacia, it has been demonstrated that optotype acuity may be near normal or normal.[42,45] Thus, visual dysfunction in periventricular leukomalacia includes a spectrum from near normal vision to severe visual impairment. However, it is important to recognize that problems in daily life for a child with visual dysfunction caused by periventricular leukomalacia are not primarily correlated to visual acuity, but are dominated by visual cognitive deficiencies.

VII. Ocular Findings

A. REFRACTION AND ACCOMMODATION

In children born preterm, myopia is a common refractive error,[39,47] and an association with ROP has been suggested.[27] In children with periventricular leukomalacia, who have escaped severe ROP, hypermetropia, often in combination with astigmatism, seems to be common.[43] The literature is sparse in describing refraction and accommodation correlated to lesions to the cerebral visual system. Hypermetropia has, however, been found in many studies on refraction in children with cerebral palsy.[2,71,75] One might speculate that disturbed ability to interpret visual information could interfere with the process of emmetropisation.

Impaired accommodation has been described in children with cerebral palsy.[55] Abnormal accommodative response was associated with low visual acuity. Hypermetropia, which would normally be latent, is made manifest, and this may be a cause of superadded amblyopia. However, insufficient accommodation may not be the only cause of lower linear acuity at near, as plus lenses do not improve acuity enough to reach the level of linear acuity at distance.[41] The problem of separating symbols on a line may be one of the major obstacles to fluent reading. It may also disable children who rely on near vision for the use of communication boards or computers as communication devices. Assessment of such children's ability to read larger text with greater separation between words and letters is warranted.

B. OPTIC DISK CHARACTERISTICS

It can be a difficult task to scrutinize the optic disk in young children with visual impairment and nystagmus. In many studies, optic atrophy or pale disks have been described in association with cerebral palsy[2] and with periventricular leukomalacia.[68,72,88] However, these findings were not confirmed by fundus photography.[68,72,88]

Brodsky et al found a link between optic nerve hypoplasia and periventricular leukomalacia.[4] The time at which the primary lesion in the optic radiation occurs seems to be of importance for the appearance of the disk. Early periventricular leukomalacia, which is often prenatal in origin, may occur before gestational week 28, and may be associated with small disks (Hellström A: personal communication).[4,42] Normal-sized optic disks with large cupping and consequently a reduced neuro-retinal rim area seem to be the consequence of later lesions, occurring after 28 weeks of gestation (Fig. 4).[42] In this developmental phase, the supportive structures of the

optic nerve have become established and probably do not adapt to the smaller number of nerve fibers.

A subnormal number of axons in the optic nerve is often, but not always, reflected by a small disk.[31] In periventricular leukomalacia, optic nerve hypoplasia probably results from synaptic degeneration of optic nerve axons caused by the primary bilateral lesion in the optic radiation. This hypothesis is based on the presence of transsynaptic degeneration of ganglion cells after a lesion of the visual cortex in very young monkeys.[9,13,89,95] In children with severe visual impairment caused by periventricular leukomalacia, degeneration of the lateral geniculate nucleus has been seen with MRI.[85] It was speculated that this degeneration was the result of transsynaptic degeneration.

Thus, there is a spectrum of optic disk appearances in children with periventricular leukomalacia, ranging from a normal-sized disk with a large cup, to normal appearance, to a small disk. Any lesion affecting the number of retinal ganglion cells before the system is fully developed should arguably be referred to as hypoplasia.[30]

C. NYSTAGMUS, STRABISMUS AND OCULAR MOTILITY

Nystagmus, which is reportedly absent in children with cortical visual impairment,[5,32] is common in children visually impaired by optic nerve hypoplasia.[31] It is also a frequent finding in children with congenital or very early-acquired ocular visual impairment with residual vision. The mechanism for this nystagmus is not known, but the development of nystagmus requires vision and some ability to fixate. Van Nieuwenhuizen described latent or manifest nystagmus in 17 of 26 children with cerebral visual impairment, many of whom were born preterm.[88] Lanzi et al reported nystagmus in 10 of 28 children with severe cerebral palsy caused by periventricular leukomalacia.[54] Nystagmus, latent or manifest of various waveforms, was registered with the Ober-2 infrared technique in 16 of 19 children with or without cerebral palsy and with visual impairment or dysfunction caused by periventricular leukomalacia documented with CT or MRI.[43] In this study, six children had clinically manifest nystagmus, while nine had clinically detectable latent or intermittent nystagmus seen with the help of a visuscope with a fixation target.

It appears that children with extensive periventricular leukomalacia and severe cerebral palsy present an ocular motor apraxia with complete disruption of ocular motor organization, including absence of fixation.[54] Children with such extensive lesions had no nystagmus or only nystagmus beats on registration with Ober-2, whereas those with milder lesions all had nystagmus.[43] Thus, it seems possible that when children with "cortical visual impairment" are selected only by severe functional deficits,[32,54] or by extensive brain lesions as detected by ultrasound, they represent one extreme of a spectrum in which manifest nystagmus does not occur. However, when children with deficits such as subnormal visual acuity, strabismus, or mild spastic diplegia caused by moderate or mild periventricular leukomalacia documented with MRI are included, they represent the other end of the clinical spectrum. These children can fixate and they exhibit nystagmus.

Nystagmus in children with periventricular leukomalacia could have several explanations. One possibility is that the injury to the immature optic radiation causes a transsynaptic retrograde degeneration that results in an anterior visual pathway lesion. Such an injury is known to be associated with nystagmus, although the causative connections have not been established. An alternative explanation for the nystagmus could be an injury to the optic radiation affecting input into the visual integrating circuits.

Defective smooth pursuit movements and inability to perform visually guided saccadic movements have been documented in children with periventricular leukomalacia.[8,43,54] It was obvious in a small group of children, when eye movements were recorded during reading, that the dysfunction in periventricular leukomalacia may include an inability to perform normal reading eye movements.[17] Three children with periventricular leukomalacia who first underwent eye movement recording and later head-movement recording during reading exhibited adaptive head movements instead of moving their eyes. Not one of these children had manifest cerebral palsy. One might speculate that this adaptive strategy is not available for children with severe cerebral palsy, as they may not be able to control their head movements. These ocular motor problems may further disturb the process of reading.

The reason for eye motility disorders remains unknown, but it is known that the dorsal stream pathway from occipital cortex to the parietal and frontal cortices subserves these functions and could be disrupted by periventricular white matter damage. This could be associated with impaired simultaneous perception in a manner akin to Balint's syndrome of oculomotor apraxia and simultanagnosia.

Strabismus in prematurely born children has been found to be associated with cicatricial ROP, refractive error, family history of strabismus, and impaired locomotor and hand-eye coordination.[67] Strabismus is also common in children with cerebral palsy.[2,22] Early-onset esotropia was most common in these groups, but exotropia also occurs. Strabismus in association with periventricular leukomalacia was demonstrated by Scher et al[72] and in most children with visual impairment or subnormal visual acuity caused by this disorder.[45,54] Children with cerebral palsy and visual

dysfunction caused by periventricular leukomalacia may have exo- or esotropia, whereas those who have escaped cerebral palsy often present with esotropia. Although normal stereopsis is rare in children with periventricular leukomalacia, a few have been orthophoric with measurable stereoacuity.[43,45]

It has not yet been possible to identify an anatomical site of damage causing early-onset esotropia. Several systems within the central nervous system appear to be important in the genesis of early-onset strabismus. One cause of infantile esotropia is thought to be an abnormality of vergence neurones[59] or of the pathways mediating eye movements.[81] The cortical areas MT and MST (areas involved in visual motion processing) may be important in the genesis of infantile strabismus.[82] Maldevelopment of the primary visual cortex has been found in monkeys with infantile esotropia.[83] A genetic or perinatally acquired defect of the horizontal connections in the striate cortex may, thus, be one cause of infantile strabismus. In addition, strabismus is frequently seen in children with defects of the eyes or anterior visual pathways disturbing the afferent input. The frequent finding of early-onset strabismus in periventricular leukomalacia may be the consequence of a deficient afferent pathway caused by axonal interruption in the optic radiation. Another possible explanation could be cortical dysfunction caused by anterograde degeneration from the primary lesion. In infantile esotropia associated with mild periventricular leukomalacia, the white matter lesion may be visualized only as periventricular signal changes (Fig. 3) or may possibly not be traceable even with MRI. Future studies of infantile strabismus with new generations of imaging techniques may provide further information about the etiology of strabismus.

VIII. Clinical Implications

A. IDENTIFICATION OF CHILDREN WITH PERIVENTRICULAR LEUKOMALACIA

Children with severe periventricular leukomalacia usually present with abnormal fixation, delayed visual maturation, and strabismus, frequently in combination with spastic diplegia and mental retardation. In these cases, the diagnosis has often already been confirmed by ultrasound in the neonatal period, or later with CT or MRI. These children, with severe functional deficits, are often already enrolled in neurological training programs.

However, the diagnosis may be a challenge in milder forms of periventricular leukomalacia, especially if the child has escaped cerebral palsy and has normal verbal development. In these cases, the pediatric ophthalmologist may be the only physician who regularly sees the child. We have seen a number of children presenting between the ages of 5 and 10 with a fairly typical set of complaints. They have previously been assessed and treated for squint with subnormal acuity. At school, they have good linguistic but poor visuospatial skills. In particular, they have difficulty accessing information from detailed work sheets. The children are "clumsy" and tend to reach inaccurately for things, and they have a tendency to trip over obstacles. In these cases, early-onset esotropia and manifest or latent nystagmus may have been the only presenting signs. A history of preterm birth in association with strabismus should make the examiner aware of the potential for a pre-existent posterior visual pathway lesion. The finding of crowding, not only in the strabismic eye but also in the best eye, is a clue to the diagnosis.[41,68] Restriction of the outer limits of the visual fields in a child with normal disks and fundi suggests a posterior pathway lesion. Large cups of normal-sized disks in a child with subnormal acuity and/or visual field defects in association with normal intraocular pressure make the diagnosis more likely.[42]

We still lack a test designed to assess visuospatial problems in children with cerebral visual impairment. A structured interview or questionnaire could be a useful tool to identify children with such problems.[16,40]

B. CONFIRMATION OF THE DIAGNOSIS

If the cause of visual dysfunction is not obvious from an eye examination in a child with nystagmus, the disease may be located in the retina or in the posterior visual pathway.[43,54,88] Unfortunately, the waveform of nystagmus does not reveal the cause.[11,43] The pattern of visual dysfunction (acuity, fields, color vision, and dark adaptation) may be of help in selecting the type of investigation, such as the electroretinogram or MRI.

A positive ultrasound in the neonatal period can confirm the diagnosis of periventricular leukomalacia. If the child has already undergone neuroimaging initially reported as normal, the diagnosis may be established if the images are reexamined with special attention to the periventricular white matter. If no previous neuroimaging examinations have been performed, MRI is the method of choice for confirming the diagnosis of periventricular leukomalacia. Neither normal ultrasound in the neonatal period nor normal CT done later excludes the presence of mild periventricular leukomalacia.[42] However, one might speculate that minute lesions in the optic radiation disturbing visual function may not be found, even with MRI. The method of choice in these cases may be the next generation of clinical neuroradiologic techniques, such as functional MRI or positron emission tomography.

C. SURGERY AND OCCLUSION THERAPY IN STRABISMUS ASSOCIATED WITH PERIVENTRICULAR LEUKOMALACIA

Amblyopia and improvement after patching have been demonstrated in strabismus associated with cerebral palsy.[22] In strabismus associated with periventricular leukomalacia, occlusion therapy improved visual acuity in the strabismic eye in a few cases with well-developed acuity in the best eye.[45] A strabismic amblyopia superimposed on the structural abnormality seen in the optic radiation may allow such improvement. Only a successful trial of occlusion therapy can confirm the presence of coexisting amblyopia.[3,53] However, patching does not improve vision in children with bilateral low visual acuity caused by periventricular leukomalacia. If occlusion therapy is started, close, periodic monitoring of visual acuity should be carried out and patching terminated if little or no improvement is detected, or if acuity in the best eye declines. It may be useful to test the monocular visual fields before making a decision about occlusion therapy. According to Yang and Lambert, a long period of enforced iatrogenic visual impairment may result in both significant psychosocial harm and developmental delay.[96] Since occlusion therapy over time in a child with cerebral visual impairment or dysfunction places considerable strain on both the child and the parents, the pediatric ophthalmologist should select cases suitable for treatment very carefully.

Hiles et al showed that satisfactory alignment could be achieved with surgery in a group of brain-damaged children with strabismus, and that only a few spontaneously reduced their angles to cosmetically acceptable ranges.[38] However, spontaneous conversion from eso- to exotropia has been seen in children with periventricular leukomalacia,[22,41] so the optimal timing of strabismus surgery probably differs from that in congenital esotropia.

D. STRATEGIES IN HABILITATION AND EDUCATION

The literature is sparse concerning the development and education of children and adolescents with cerebral visual impairment. In our experience, it is helpful to reduce the amount of surrounding visual stimuli in order to decrease crowding, thus allowing the child to use vision optimally. Enlargement of the text to a size at which the child feels most comfortable improves the rate at which printed material can be accessed. It is important to find the strategies that the child has learned to use, to add strategies if needed, and to facilitate the use of them. The school staff and family all have to be aware that the child may need to use compensating strategies, such as identification by sound or color and the use of verbal maps.

Orientation is sometimes a severe problem and the child may need to use a cane for mobility. Alternative reading media such as talking books, computers with synthesized speech, and in a few cases, Braille (Fellenius K, personal communication) have to be considered. Structured and calm surroundings facilitate the child's learning. It is also important to enhance access to visual material with the help of color marking, enlarging computer programs, closed circuit television (even for children with a visual acuity above 20/60). In children who cannot interpret written symbols, even though they may be able to pronounce, identify, and put letters together to synthesize words by sound, reading of print may be unattainable.

Children with visual impairment caused by periventricular leukomalacia need a multidisciplinary assessment.[45,76] Such an assessment requires cooperation between pediatric ophthalmologists, orthoptists, pediatric neurologists, neuroradiologists, psychologists, and teachers. A thorough examination of visual and motor function and of the intellectual profile may form the basis for an adequate habilitation and adapted education. Knowledge of abilities, as well as disabilities, in verbal and performance tasks helps to identify suitable strategies to solve everyday visual problems. It certainly also helps the parents to understand the sometimes puzzling and often awkward behavior of their child.

IX. Conclusion

Periventricular leukomalacia is a frequent cause of visual impairment in children born prematurely. Children with periventricular leukomalacia often have a concomitant spastic diplegia. These children may present to the pediatric ophthalmologist with early-onset strabismus. Their intellectual profiles are often uneven, and visuospatial problems are frequently observed. Delayed visual maturation, subnormal visual acuity, crowding, visual field defects, and cognitive visual dysfunction characterize visual function. Periventricular leukomalacia may cause strabismus, nystagmus, and eye movement disorders combined with complex cognitive disorders of vision. Optic disk hypoplasia with subnormal rim area (small disks or large cupping of normal-sized optic disks) may be a consequence of retrograde transsynaptic degeneration and reflect the timing of the brain lesion. Habilitation and education need to be adapted for children with visual dysfunction caused by periventricular leukomalacia, even those with fairly well developed visual acuity, with consideration of impaired visual input as well as deficient processing of visual information.

Methods of Literature Search

MEDLINE/Pub Med and Ovid databases were searched, covering the years 1966 to 1999, and ap-

propriate citations were reviewed. Search words comprised *periventricular leukomalacia, risk factors, cortical visual impairment, cerebral visual impairment, cerebral palsy, strabismus, nystagmus, optic nerve hypoplasia.* Additional references were obtained from the bibliographies of articles obtained from the MEDLINE search. Other sources included standard textbooks. The one non-English article was in German and was read in the original language.

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Outline

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The authors have no proprietary or commercial interest in any product or concept discussed in this article.

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