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REVIEW ARTICLE

Delayed visual maturation in infants

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Abstract

Delayed visual maturation (DVM) is the condition wherein infants who appear blind at birth regains normal or near normal vision with time. We describe the modes of presentation along with an approach to the visually inattentive child and a differential diagnosis of the condition. We discuss the electrodiagnostic findings and indications for further investigation. The pathophysiology of DVM is not known, but it may be due to a fault of the sensory, motor, or visual attention systems, and these hypotheses are described in detail. Finally, the term "temporary visual inattention" is proposed as a more accurate term that best describes our current understanding of DVM.

Introduction

The term delayed visual maturation (DVM) has been used to describe infants who initially appear blind, but in whom, with time, normal or near-normal vision develops.[1] The diagnosis may be reserved for infants with visual inattention who have an otherwise normal ocular and systemic examination; however, some authors use the term more loosely to describe any infant with apparently poor vision that shows some signs of improvement.[2] Since the original description of DVM,[3] a classification system has evolved.[4-6] The classification system aims to group children according to other ocular or systemic abnormalities and therefore enable a better prediction of prognosis.

More recently, our understanding of the basis of DVM has improved, and the use of the term DVM has been questioned.[2] The term DVM suggests that the cause for visual inattention in these children is a delay in the normal process of development in the visual system. There is little evidence to support this notion; in contrast, many children with visual inattention develop other neurodevelopmental problems. We support the view of Hoyt[2] that the term temporary visual inattention best describes our current understanding of this condition.

Definition and Classification

In 1947, Beauvieux initially reported that children who were apparently blind could show complete visual recovery.[3] The term DVM was first suggested by Illingworth in 1961 when he described two infants with normal ocular examination who displayed visual unresponsiveness before the age of 6 months and who then became attentive to visual stimuli after this age.[4] DVM has previously been referred to as temporary visual inattention, la pseudo-atrophie optique des nouveau-nés,[3] papilla grisea,[7] myelogenesis retarda,[8] dissociated visual development,[8] and visual developmental delay.[5,6]

Based on the presence or absence of associated abnormalities, Beauvieux considered DVM to exist in two forms.[3] In type 1 DVM, the delay in visual maturation was an isolated finding, and full visual recovery could be expected by 4 months of age. In type 2 DVM, there was an associated problem such as nystagmus or mental retardation, and in these cases, visual recovery was slower and less complete.[3] DVM may be associated with other ocular and systemic abnormalities such as albinism, prematurity, or perinatal insult.[6,9,10]

A further category was later introduced by Uemera allowing specification of whether the associated abnormality was ocular or non-ocular.[5] Uemera proposed that type 2 DVM should

include infants with DVM who are mentally retarded or have a seizure disorder and type 3 include those with a primary visual abnormality.[5]

In 1985, Fielder *et al.* examined the clinical features of 53 infants from 3 centers with DVM.[6] A modified classification of DVM was proposed based on Uemera's classification with two subcategories of type 1 DVM.[6] Infants classified as type 1A were those with a normal peri-natal history, while infants classified as type 1B had a history of perinatal problems. Group 1A was further subdivided into 1Ai to include infants with poor vision on presentation and group 1Aii for those whose vision had already improved by the time they were assessed by an ophthalmologist. Similarly, to the classification of Beauvieux,[3] DVM type 2 was associated with non-ocular abnormalities such as mental retardation. A final type was identified as DVM type 3 to include those children with stable ocular abnormalities whose vision was worse than could be attributed to the ocular problem alone and who demonstrated an improvement of vision within a short period of time.[6] In 1991, Fielder and Mayer introduced a type 4 category of DVM by classifying children with albinism and idiopathic congenital nystagmus as type 3 and those with other severe ocular disorders as type 4 [Table 1].[11]

The evolving classification system was complex and had questionable value. Recently, it has been suggested that we revert to the original term "temporary visual inattention."[2] Temporary visual inattention is a term applied to a clinical situation in otherwise healthy infants, who are initially visually inattentive but become completely responsive by 4–6 months of age. In these children, there is no other known ocular or central nervous system (CNS) disorder. Despite the move away from the broad definition of DVM, an understanding of previous classifications of DVM is necessary to adequately analyze the literature. Previous studies of visually unresponsive children have included patients with coexistent ocular and non-ocular conditions who would not be considered to have simple DVM by today's standard.

The term DVM implies that there is a delay in a normal process of the development of the visual system. Before considering DVM, further it is helpful to consider the normal development of the human visual system.

Table 1: Historical classification of delayed visual maturation

Classification	Description Delayed visual maturation with
Group 1	
A	No other abnormality i. Poor vision on presentation ii. Vision already improved
B	History of perinatal problems
Group 2	Mental retardation
Group 3	Albinism, idiopathic congenital nystagmus
Group 4	Other severe ocular disorders

Normal Development

Normal development of the visual system

The development of improved visual acuity from infancy to adulthood can be explained by the development of the visual system, which is far from maturity at birth. In the following discussion, the maturation of each component of the visual system is considered separately.

Photoreceptors

The retinal photoreceptor cells are formed by 24 weeks gestation; however, at birth, they are still developing.[12,13] The neonatal fovea is anatomically immature. Cones do not reach adult dimensions until 14 months after birth and foveal cone density develops even more slowly not reaching adult levels until a few years of[14,15] Despite structural immaturity, electrophysiological tests suggest that cones are functionally mature at birth.[16-18]

Ganglion cells

The retinal ganglion cells are also immature at birth.[19] In the mature retina, the retinal ganglion cells may respond to light increments (on cells) or light decrements (off cells). The dendrites of the on- and off-center retinal ganglion cells are stratified in the different lamina of the inner plexiform layer. In contrast, in the immature eye, the immature ganglion cell dendrites are found throughout the inner plexiform layer.[19] Studies of the development of optic nerves have shown that myelination of the anterior visual pathways increases up to 2 years of age.[20] Cortical dendrite growth and synapse formation also continue during the first 2 years of life.[21] If the visual pathways are immature at birth, it is predictable that the visual evoked potentials (VEPs) are also immature. Children <3–5 months of age have been shown to have a delayed VEP latency compared to adults.[22,23] Postmortem studies on premature infants have shown that the maturation of the VEP correlates with the degree of cortical dendrite formation.[24]

The cortex

Development of the visual cortex has been studied extensively in Macaque Monkeys. The lateral geniculate nucleus develops at 8–11 weeks and acquires characteristic lamination between 22 and 25 weeks gestational age with concurrent development of the striate cortex. Formation of ocular dominance columns develop between 26 weeks and term, and cortical development continues postnatally with the majority of interconnections in the striate cortex complete by 8 months postnatal age.[25]

After birth, sensory experience and spontaneous activity play a role in the development and remodeling of the retinal neural circuit.[26] Spontaneous activity is thought to drive synaptic refinement around the time of eye opening, while sensory experience is important for the maintenance of these connections.[27] Some types of developmental delay have been attributed to delays in myelination of the brain; however, there is no evidence to support this in DVM.[28]

Normal formation of the visual cortex is thought to be controlled by subplate neurons in the subependymal germinative zones.[29] The subplate neurons release neurotrophins that guide geniculocortical afferent neurons toward the appropriate cortical

target cells.[30] Subplate neurons also provide a site for synapse formation for axons ascending from the thalamus and other cortical sites.[31]

Synapse formation in the subplate neurons occurs between 22 and 34 weeks of gestation; however, at this stage, the cortical plate is not fully developed.[32] The ascending afferent pathways are held by the subplate neurons near the germinal matrix until the cortical plate has matured. The brain and blood supply to the brain in a preterm infant are different compared to a term infant.[33] The germinal matrix has fragile blood vessels, which are vulnerable to changes in blood pressure.[33] Premature infants may be more vulnerable to hypoxic insults that lead to visual problems. Studies in premature infants indicate that, if the subplate neurons are damaged, cortical structures, including the ocular dominance columns, may fail to develop normally.[34,35] It is not known if prematurity increases the risk of DVM.[36] Although subplate neuron dysfunction may explain visual impairment in some premature infants, there is no evidence to support a role in DVM in children who are otherwise normal. Subplate neuron dysfunction is not supported by the normal VEP studies in infants with DVM, compared to age-matched controls.

Cortical maturation during the first few months of life has been demonstrated by electroencephalogram studies. During early infancy, there are substantial changes in the electroencephalography (EEG) which are so predictable that they can be used to estimate an infant's gestational age to within 1 week.[37] It is at around 3 months of age that the saw-tooth wave characteristic of the adult EEG during the rapid eye movement phase of sleep begins to appear. Shortly following this, the EEG shows a 3–4 Hz 50–75 MV occipital rhythm when the child is awake which eye-opening interrupts. The frequency of this gradually increases to 6–7 Hz by 5 months of age.[37]

The motor system

Normal visual maturation also depends on maturation of the motor system. For example, there is a period of postnatal maturation in the mechanisms that allow ocular motor stability. Some infants develop transient idiopathic nystagmus during this period.[38] As ocular motor stability improves, the nystagmus disappears. During this period, nystagmus may appear and then disappear.[38] Bianchi *et al.* described two children with wide-amplitude and high-frequency nystagmus who had poor visual awareness.[39] By 5 months of age, nystagmus was no longer detectable and both infants appeared to be visually, developmentally, and neurologically normal.

Visual acuity in infants

It is now possible to obtain quantitative measurements of visu al acuity in infants by behavioral or electrodiagnostic techniques. Both methods have revealed that infant's vision is reduced compared to adults.[40,41] Preferential looking tests are based on the presentation of gratings of different spatial frequency. When the infant is confronted by the grating and a blank stimulus, the infant is expected to preferentially look at the latter. The grating acuities are recorded in cycles per degree with 3c/° equivalent to 6/60 and 30c/°to 6/6.[41] Neonates have been estimated to have visual acuities of approximately 6/60–6/120. By 6–8 months of age, this has improved to 6/12.[40,41] Components of visual acuity include grating acuity, Vernier acuity, and contrast sensitivity. Grating acuity is a measure of the finest resolvable detail, and Vernier acuity is a measure of sensitivity to relative positions. Contrast sensitivity is calculated from the contrast threshold, which is the lowest detectable contrast of a given grating. Each component of vision has a different developmental course, whether measured by preferential-looking or electrodiagnostically.[42] Contrast sensitivity develops rapidly, whereas grating acuity is slower to mature and Vernier acuity does not reach maturity until adolescence.[43] Early preferential looking studies suggested that Vernier acuity was superior to grating acuity by 4–5 months of age.[42] However, these studies were flawed as they used temporal stimuli in Vernier testing and stationary stimuli in the grating tests. Zanker *et al.* assessed Vernier and grating acuities using stationary targets and found that Vernier acuity was better than grating acuity only after 4 years of age.[44] An analysis of several studies has found that Vernier acuity reaches adult levels between 5.7 and 8.7 years of age and resolution acuity between 1.4 and 2.2 years of age.[43] Good *et al.* found that two infants with DVM had normal Vernier acuity for age.[45] The finest resolvable acuity is limited by the density of foveal cone photoreceptors which is known not to reach adult levels until several years of age.[46] As the receptor size and spacing matures, the cortex receives finer information.[46] Grating acuity during the 1st month of life is approximately 4.5 c/°, increasing to 20 c/° at 8–13 months.[47] Norcia *et al.* found that, by 8 months of age, the VEP grating acuity was not reliably different from adult levels.[47] Skoczenski *et al.* also found that grating acuity matures quickly but in contrast to Norcia *et al.*, at 50 weeks of age, grating acuity was still less than adult levels.[48] Vernier acuity thresholds are markedly immature during the 1st year of life. By 50 weeks of age, they are still 10 times lower than adult values.[48] With development, there are changes in retinal receptor size and density and a corresponding improvement in grating and Vernier acuity.[49] The different components of visual acuity may be affected to a varying degree by different conditions. For example, in amblyopic eyes, contrast sensitivity is relatively preserved, and there is a moderate reduction in grating acuity but a large reduction in Vernier acuity.

Quantitative techniques have allowed us to better appreciate the normal process of visual development. It is not clear what effect DVM might have on each of these components of vision.[50]

The maturation of the VEP

Studies in pre-term infants have also allowed research into the maturation of the VEP.[51] With increasing age, the latency of the Pl00 VEP decreases.[20] Postmortem studies have shown that changes in the VEP latency correlate to an increase in myelination. The waveform components of the VEP have also

been shown to be affected by factors such as maternal smoking and fetal growth retardation.[52]

Developmental Delay

A delay in development is thought to affect 5–10% of children.[53] Delay may affect gross and fine motor skills, speech and language, cognition,personal and social development, and activities of daily living. Normal childhood development may proceed at different rates, and there is no consensus on the specific definition of developmental delay. Significant developmental delay, however, is defined as a child which is 2 standard deviations behind the mean in the age of reaching a developmental milestone.[53] Global developmental delay is a delay in two or more spheres of development. Causes of developmental delay can be genetic (e.g. chromosomal abnormalities), neurological (cerebral injury or malformations), metabolic, toxic, endocrine, or environmental. Ocular abnormalities including refractive errors and strabismus have been found in 13–25% of children with global developmental delay.[54] DVM may be an isolated defect or occur in association with delays in other spheres of development. Children with poor vision in one eye (e.g., enucleation due to retinoblastoma) generally function normally in terms of physical health and mental and motor development; however, children who have bilateral visual impairment are more likely to be delayed developmentally.[55]

It is well recognized that children with DVM may have delays in other developmental milestones. There seems to be a relatively high prevalence of developmental delay in children with DVM. This suggests a generalized neurological problem. Lambert *et al.* found that four of the nine children they studied were delayed in achieving motor milestones.[56] One of these children had global developmental delay at 3 years of age. An magnetic resonance imaging (MRI) scan of the brain showed cortical atrophy and a thalamic lesion. Fielder *et al.* found a delay in orientation to sound[6] and seven of eight children studied by Hoyt had general motor delay.[9]

Modes of Presentation

Infants with DVM show poor visual behavior and are unable to fixate and follow a light or respond to preferential looking cards. Aside from poor visual responses, their ocular and systemic examination is normal. Lambert *et al.* reported a mean age at presentation of 3.4 months in their series.[56] Infants became visually response at a mean of 5.5 months (range 3–8 months).[1] In Fielder's series of 42 infants with type 1 DVM, the median age of visual responsiveness was 14 weeks of age; however, infants with type 1A responded at 9–18 weeks of age, while infants with type 1B were 11–40 weeks of age.[6,11] Infants with type 2 DVM often have significant associated structural CNS pathology, demonstrable on neuroimaging. This is frequently accompanied by a seizure disorder and may be related to birth trauma or other insult. Sometimes, the visual responsiveness of a child with type 2 DVM improves with control of the seizures.[57] The improvement in vision in these patients is slower, later and often less complete than for infants with type 1 DVM.[6] Infants with type 3 DVM have an associated ocular abnormality such as nystagmus, albinism, or cataract; however, their vision is worse than would be expected from the disease alone. Children with type 3 DVM have a slower and later improvement in vision than those with type 1 DVM. In Fielder's series, the median age of improvement was 20 weeks for children with ocular abnormalities.[6] A high frequency, wide amplitude, transient jerk nystagmus that improves as visual responsiveness improves has also been reported in patients with DVM.[39] It follows that the prognosis for vision in these children depends on the underlying ocular abnormality.

An Approach to Child Who is Visually Inattentive

History

Children with DVM may present due to parental concern or following routine screening. A detailed visual history including time of onset of reduced vision, time and speed of visual recovery, and associated visual and ocular symptoms is important. Other data collected included sex, ethnicity, and details of the pregnancy, birth weight, perinatal period, and the infant's subsequent development including age at onset of smiling. The comprehensive history should include a detailed prenatal, perinatal, and postnatal history. Ask the mother about drug ingestion or systemic infection during pregnancy. It has been suggested that DVM might be caused by gestational nutritional deficiency or toxins leading to delayed cortical myelination or parietal cortex structural defects.[58] Ascertain whether there has been developmental delay or regression.

The parent's assessment of their child's visual behavior is helpful but not always an accurate reflection of the child's true visual acuity. Tressider *et al.* found that some parents did not think that their child could see until the visual acuity was 3.0 c/° ,whereas others thought that they could see at 0.2 c/°.[59]

Examination

The examination of the child should include an assessment of vision, qualitatively by the fixation and following response to a light, toy, or face, and if possible quantitatively using preferential looking techniques. There should be an assessment of ocular motility, pupillary reactions, refraction, and dilated fundoscopy. It is important to test the brainstem saccadic function of any child with poor visual behavior. Harris *et al.* have shown that binocular OKN is normal in children with DVM; however, the monocular OKN is asymmetrical.[60] Lambert *et al.* found that infants with DVM had poor nasotemporal following.[56] The vestibuloocular response (VOR) is usually normal; however, Hoyt and Eviatar have shown that preterm infants with normal visual behavior may lack a fast-phase component to vestibuloocular testing.[9,61] The fast phase became presented by 1 month of age. If saccadic testing is abnormal, an MRI scan of the brain is indicated. Examine the child for dysmorphic features. Early studies of DVM thought that the pupil responses were absent.[7] Another

study concluded that both behavioral and pupillary responses to gratings were delayed in DVM, indicating that although the underlying defect is primarily subcortical, secondarily it delays the emergence of cortically mediated responses.[62]

Investigations

The investigations required for a visual inattentive child depend on the age of the child, duration of visual inattention, examination findings, and whether there is delay in any other developmental domains.

Systemic investigations should be considered, especially if there is a delay in more than one developmental sphere. For example, the first-line investigations for global developmental delay might include chromosomal analysis, full blood count, urea and creatinine, creatinine kinase, lead toxicity screening, thyroid function tests, urate (for purine disorders), and ferritin. These investigations are best done in conjunction with the pediatrician in addition to a thorough systemic examination.

An EEG and neuroimaging should be done if there is a history suggestive of seizures, an abnormal head size, or focal neurology or if the poor vision persists beyond 6 months of age. Metabolic tests may also be considered as should referral to the genetics department.[63] The assessment of visual acuity in infants is not always easy. Many of the clinical methods rely on an intact sensory and motor system. Interestingly, children with DVM, although seemingly having visual inattention, may have good grating and Vernier acuities. Vernier and grating acuity thresholds, measured electrophysiologically, were normal in two children with DVM even though their visual behavior was deemed abnormal.[45]

Visual unresponsiveness in children may be due to uncorrected refractive error; therefore, retinoscopy in any case of suspected DVM is essential. Winges *et al.* described two patients aged 4 and 5 months who were felt to have DVM.[64] On refraction, these infants had 4–9 diopters of myopia. When the myopia was corrected, the children had normal visual behavior. Another test to consider is a hearing evaluation.

DVM has been associated with auditory neuropathy/dyssynchrony, a condition of hearing impairment associated with absent or severely abnormal brainstem auditory evoked potentials but normal cochlear functions. Aldosari *et al.* described a single case and suggested that a detailed hearing evaluation should be performed for all children with DVM.[65]

Some investigators have found children with DVM to have abnormalities on neuroimaging. This may be attributed to many of these patients having type 2, 3, or 4 DVM. Hoyt *et al.* found that 5 of 14 patients with type 1 DVM had abnormalities on MRI.[9] Fielder *et al.* and Russell-Eggitt *et al.* have suggested that some children with type 1 DVM may have suffered unrecognized perinatal insult.[11,66]

Fielder revisited the patients he had originally labeled as type 1A DVM and found that 6 out of 16 had actually had perinatal problems.[11]

By definition, neuroimaging of children with type 1 DVM is normal. Some studies have reported abnormalities, but there are certainly no consistent findings.[1,67] We recommend neuroimaging only in cases where other ocular or systemic anomalies are present or suspected.

Electrodiagnostics

Electrodiagnostic tests including flash visual evoked response (VER) and photopic and scotopic electroretinography (ERG) may be performed. The assessment of visual acuity in infants in the clinic depends on both sensory and motor systems. Electrophysiological tests assess the sensory system alone and are a useful tool in children with DVM. Electrodiagnostic tests do not rely on the infant's ability to generate an appropriate behavioral motor response.

Most authors are in agreement that infants with DVM have a normal ERG. Fielder *et al.* found normal ERGs in all 33 cases of DVM that they tested.[6,11]

In contrast, several authors have described abnormal flash and pattern VEPs in infants with DVM.[8,9] Abnormalities of VEPs have included prolonged latencies, abnormal waveforms, and decreased amplitudes. Mellor reported an absence or delay of flash VEPs in four children with DVM.[8] Maturation of the VEP was seen as visual responsiveness improved.[8] Harel had studied three children with DVM, all of which had delayed latency of their VEPs. By 6 months, the children had normal vision and normal electrodiagnostic investigations.[68] Kraemer *et al.* also reported a series of children with initially abnormal flash VEPs that improved as an appropriate visual response developed.[69] In 1983, Hoyt described a series of 8 children with DVM. 7 of the children also had delays in motor development. 6 of the children had been premature or low birth weight. In each child, there was a normal ERG, but the pattern onset-offset VEP was absent or attenuated.[9] Fielder and Russel-Eggitt found that 78% (32/41) of children with DVM that they investigated had abnormal flash VEPs.[6] The abnormalities included abnormal waveforms, prolonged latency, and decreased amplitudes.

A major limitation of the majority of the VEP studies is that the electrodiagnostic responses of these patients with presumed DVM were not compared with age-matched controls. Visual function, assessed by VEP, varies among normal healthy newborns. The VEP is initially of long latency and duration before it becomes more compact and of shorter latency. A more mature VEP develops by approximately 5 weeks of age corresponding to the development of responsive smiling and responsive visual behavior. Therefore, a normally developing infant may be expected to have some change in VEP as they mature. Previous studies in healthy children have shown a prolonged latency of flash and pattern VEPs compared to adults.[40,70] Therefore, the abnormal latency in children with DVM may be normal for their age and the changes in latency over time may reflect normal maturation.

Indeed, compared to adults, healthy neonates have been shown to have prolonged latency of the P100 of the flash and pattern-reversal VEP. Maturation does not occur until up to 6 months of age.[26] Normal infants also have decreased VEP amplitudes, which mature more slowly than VEP latency.[71]

Lambert *et al.* conducted a prospective longitudinal study of nine infants with presumed isolated DVM.[56] The ERGs and VEPs of the infants with DVM were compared to age-matched controls. Eight of nine patients had normal flash and pattern VEPs, and all of the children had normal ERGs. Children aged <3 months were found to have a prolonged P100 latency; however, there was no significant difference when these children were compared normal children of a similar age.[56]

Discrepancies in the VEP studies may be due to the heterogeneous nature of DVM. Russell- Eggitt *et al.* suggested that some children with DVM may have had resolved periventricular hemorrhages, a known cause of immature and delayed VEP waveforms.[66] A further difficulty in the interpretation of electrodiagnostic tests is the wide variation in the normal waveform. In summary, electrodiagnostic tests may serve as a prognostic marker in DVM. While the presence of a normal VEP is reassuring an abnormal pattern or even flash VEP does not mean, the baby will not see.

Differential diagnosis

The differential diagnosis of the apparently blind child with a normal examination includes:

Cortical visual impairment

Cortical visual impairment is an important cause of visual unresponsiveness in children. This may be permanent or temporary. The term cortical visual impairment is misleading because in most cases it is the insult to deep subcortical white matter (periventricular leukomalacia) that is responsible for the visual impairment. For this reason, the term "cerebral visual impairment" has been suggested as a replacement.[72]

Cortical visual impairment is characterized by the infant with poor vision, no nystagmus, and a normal eye examination, including normal pupillary light reactions and unremarkable fundi (at least initially). It may, however, be accompanied by restricted visual fields, reduced accommodative function and disorders of ocular motility including strabismus, nystagmus (which is a common accompaniment of periventricular leukomalacia), dystonic eye movements, and disorders of pursuit and saccade.[73]

Good *et al.* have extensively reviewed cortical visual impairment.[74] Prognosis for recovery depends on etiology, age of onset, and severity of brain damage. Cortical visual loss from perinatal hypoxic-ischemia has a particularly poor prognosis if congenital, but up to a 70% recovery rate if acquired.[10] Investigations including VEP, OKN and neuroimaging are often abnormal unlike in infants with DVM. Children with cortical visual impairment may demonstrate some improvement in vision. For example, Lambert *et al.* reported on visual recovery from hypoxic cortical blindness.[75]

These children can also have associated neurological defects that require ongoing management and interfere with visual function. Some children may have transient cortical blindness due to seizure activity. Seizure activity can also affect cortical visual attention mechanisms.[76,77]

Ocular motor apraxia

Eye movement abnormalities may be misinterpreted as poor vision as assessment of visual behavior in infants is to large degree interpreted based on visually directed ocular movements. Congenital abnormalities of saccades may be due to CNS abnormalities, lipid storage disorders, or perinatal insults; however, if no abnormality is found, this is termed ocular motor apraxia. Children with abnormal saccades compensate using horizontal head thrusts to overcome the lack of saccadic drive to follow a target. This compensatory mechanism takes time to develop, and until then, children may appear visually unresponsive. Demonstration of vertical saccades or pursuit responses, OKN responses in any direction, or normal visual acuity on VER testing may confirm the diagnosis of congenital ocular motor apraxia.[78]

Retinal dystrophies

Leber's congenital amaurosis is an autosomal-recessive retinal rod/cone disorder that causes poor vision from birth and may be confused with DVM. Although initial fundus examination may be unremarkable, pigmentary retinopathy, vessel attenuation, and optic atrophy occur over time.[79] The ERG shows unrecordable or grossly attenuated electrical potentials of both rods and cones (the "flat ERG"). No treatment is available for this condition. Achromatopsia (rod monochromatism) is an autosomal-recessive or X-linked disease characterized by a partial or complete absence of retinal cone function. Visual acuity is generally better than in Leber's amaurosis and frequently exceeds 20/200. In this condition, the rod ERG is normal, whereas the cone ERG is significantly impaired. Photophobia, which may be marked, is quite common, and these children show a marked preference for dim lighting.[79]

Global developmental delay

DVM may be due to global developmental delay as discussed previously.

Epilepsy and drugs

Children with type 2 DVM often have epilepsy; however, a child who is experiencing frequent seizures or is being treated with sedatives may also appear visually unresponsive. Once the epilepsy is optimally controlled, these children may become more responsive. DVM has also been described in children whose mothers were users of cocaine during pregnancy.[80]

Associated findings

Most of the series demonstrate that children with DVM will develop normal vision; however, the recovery period and eventual outcome depend on the underlying cause and associated features of DVM. Tresidder *et al.* investigated 26 children and divided them into four groups (type 1A, type 1B, type 2, and type 3 DVM).[59] Tresidder found the age at which visual improvement began differed in each group. For type 1A, vision improved at 10–18 weeks of age (mean 15 weeks), for type 1B, at 7–34 weeks (mean 15.7), for type 2, at 22–78 weeks (mean 45.7), and for type 3, at 13–28 weeks (mean 24).[59] Therefore,

infants with type 3 DVM, with nystagmus or other ocular defects, attained normal vision but had a slower recovery than infants with type 1 DVM. Infants with type 2 DVM had persistent neurodevelopmental abnormalities and did not develop normal vision. Appropriate visual development is not the only concern when assessing children with DVM. Further follow-up of cases of isolated DVM type 1 have shown delays in other developmental milestones such as walking.[3,10,53] This observation suggests that DVM is more complex than just delayed visual behavior.

Delayed developmental milestones

Hoyt found that 7 of 8 patients with DVM also had delayed motor development.[9] Cole and Fielder have described children with DVM who are also slow to speak and hear.[10,11] In Fielder's description of 53 infants with DVM, there was a delay in hearing reported in 6. The onset of smiling was delayed beyond 6 weeks of age in 31 children.[6]

Neuropsychiatric disorders

Recently, Hoyt has reported a series of 98 patients with isolated DVM.[2] 93% of infants in this series eventually developed a best-corrected visual acuity of 20/20 or better. In contrast, many of these children were subsequently diagnosed with neuropsychiatric disorders including 22 patients with learning difficulties, 11 with attention deficit disorder, 4 with autism, and 5 with other psychiatric disorders. Nine patients subsequently developed seizure disorders and 5 had cerebral palsy. An interesting aspect to DVM is that many children who are initially felt to have an isolated delayed development in vision have been found on follow-up studies to have evidence of other neurological damage.[6,9,10] Hoyt had suggested that we should not use the term DVM as this implies that DVM is an isolated prolonged normal maturation.[2] Some children with DVM who seem otherwise normal later develop neurodevelopmental problems. It has been suggested that abnormal vision might indicate neurological impairment due to a perinatal insult. In Lambert's study, children with DVM became visually responsive at a mean age of 5.5 months.[56] Lambert *et al.* suggested that DVM is due to an abnormality of the visual association areas. Tresidder *et al.* also conducted a prospective study.[59] They examined 26 children and found that those with isolated DVM had the earliest onset of visual improvement. Those that had a perinatal insult had a slower recovery and one-third developed a neurodevelopmental abnormality.

Other ocular abnormalities

Strabismus is very common during the period of visual inattentiveness. Tresidder found that all infants with type 1A DVM had strabismus.[59] In contrast, and by definition, nystagmus is not a feature of type 1 DVM, although Tresidder *et al.* found that patients with type 3 DVM developed nystagmus around the time of visual improvement.[59] Fielder found that 15 of 29 patients with DVM also had a divergent squint, 8 were convergent, and only 6 orthotropic.[11] With follow-up, all of the divergent squints resolved but only one of the convergent squints. Bianchi *et al.* had reported two cases of children with apparent visual inattention who also had nystagmus.[39] The first child presented at the age of 3 months with horizontal jerk nystagmus with high frequency and wide amplitude. By 5 months, the nystagmus was resolving and visual behavior had improved. By 8 months, the nystagmus had disappeared completely. The second patient presented at 2 months, unable to fix, and following. There was also jerk nystagmus with a vertical component. At 4 months of age, the nystagmus had almost disappeared and visual awareness was almost normal. The nystagmus in both consisted of horizontal jerks and a vertical component.[39]

In a further study, Fielder and Tressider examined 26 infants with DVM.[59] The visual acuity of these children was assessed using the acuity card PF procedure. Of 26 infants, only 8 had isolated DVM with no perinatal problems (although 3 of these children were preterm). In 8 children with isolated DVM, visual improvement occurred at a mean of 15 weeks of age (range 10–18 weeks). Once vision had begun to improve, normal levels of vision were reached rapidly. For 7 of 8 infants, normal vision was achieved between 12 and 17 weeks of age. Fielder *et al.* found that patients in Group 1 had a rapid improvement in vision often over just a few days and at a median age of 14 weeks.[6]

Prognosis

The prognosis of a child with DVM depends very much on the definition of DVM chosen. Children with associated ocular and systemic problems can be expected to have a slower and less complete recovery. Children with isolated DVM recover vision during a narrow time frame. Cole *et al.* also conducted a prospective study of 16 children with DVM.[10] All of these children developed visual responsiveness between 4 and 6 months of age. However, some of the children developed neurological abnormalities after long-term follow-up. Children with cortical or ocular abnormalities may show some visual recovery. Roland *et al.* found that 50% of children with visual impairment due to birth asphyxia had some degree of visual recovery.[81] Children with ocular disorders who initially appear blind may also show some improvement in vision. In Fielder's series of 11 patients with conditions such as coloboma and optic nerve hypoplasia, 8 children showed visual improvement.[82] Evidence suggests that children with DVM often do not have an isolated, temporary visual problem. Goodman *et al.* described 3 boys who presented with DVM which spontaneously resolved.[83] However, they later developed severe autistic impairment, general developmental delay, hypotonia, and clumsiness. It was proposed that a widespread delay in brain maturation could account for this.

Several authors have noted a high incidence of prematurity in children with DVM.[3,6] It has been suggested that some children with DVM may have had undetected neurological insults.[66] Fielder *et al.* reexamined their original DVM study population and found that many of the children originally thought to have Type 1a DVM had actually had a history of perinatal trauma. An interesting study was conducted by Hungerford *et al.* 177

preterm infants born at <33 weeks' gestation were examined.[33] This study was unusual compared to other studies of DVM in that the children received repeated cerebral ultrasound scans, daily for the 1st week of life, and a regular interval thereafter. 9 (5%) children were diagnosed with DVM. 7 of 9 children were found to have periventricular hemorrhages on ultrasound scanning. 2 had evidence of hypoxic-ischemic brain injury. 5 children had neurodevelopmental disorders at follow-up. Hypoxic-ischemic injuries are closely associated with neurodevelopmental problems.[85] If children with DVM had unrecognized hypoxic injuries, this might explain the high incidence of neurodevelopment problems in these children.

Discussion

The etiology of DVM

Several authors have found a high incidence of perinatal problems in patients with DVM and have suggested that DVM may be secondary to perinatal hypoxia or hemorrhagic insults which may not have been apparent at the time.[9] In some studies of DVM, infants that initially seemed normal (type 1 DVM) have later developed neurological problems and have been shown to have structural abnormalities on neuroimaging.[59] In the series by Hoyt *et al.*, one-third of patients with type 1 DVM were later found to have structural abnormalities on MRI.[9] Other authors have argued that patients with structural abnormalities should not be classified as having DVM.[66]

The pathophysiology of DVM

The pathophysiology of DVM is not known; however, several theories have been proposed. Each component of the visual system has been considered as a casual candidate for DVM. DVM may be due to a fault of the sensory, motor, or visual attention systems. The fault may represent a delay in normal development or a pathological process.

Cortical and subcortical pathways

It has been proposed that DVM may be a disorder of the subcortical visual pathways. Children with DVM tend to recovery between 3 and 5 months of age and often over the period of just a few days. These improvements occur at around the time some cortical functions are thought to emerge.[11,59,62] Some electrophysiology studies of children with DVM have shown prolonged latency on VEP. When visual interest and responsive smiling develop, there is maturation of the VEP.[69] In developing animals, geniculocortical and extrageniculate visual afferent pathways evoke two types of VEPs. The VEP responses seen in infants have been noted to be similar to recordings from children with lesions of the geniculostriate pathway or primary cortex.[84-86] This observation has led to the understanding that extrageniculate visual afferent pathways mature before the geniculocortical system and that vision in early infancy is mediated by subcortical pathways. Cortical processes develop by 3 months of age, which is often the time of improvement in DVM. It has been suggested that DVM has a subcortical basis.

Investigators have tried to measure the function of the cortical and subcortical systems separately in children with DVM. Pupil responses to gratings reflect cortical activity alone and normally become measurable at 1 month of age. In contrast, the acuity card procedure reflects both subcortical and cortical function and can be detected at birth. In one infant assessed by Cocker *et al.*, the development of both behavioral and pupillary responses was delayed.[62] This implicates both the subcortical and cortical visual systems in DVM. In the normal developing visual system, VEP Vernier acuity and grating acuity develop at different rates. Grating acuity approaches adult levels earlier than Vernier acuity.[48] Vernier acuity is believed to be cortically mediated and has been shown to be relatively lower than grating acuity in children with cortical visual impairment. Normal Vernier acuity in children with DVM suggests normal cortical function.[87]

Cocker *et al.* studied the possible roles of the cortical and subcortical visual systems in a DVM twin study.[62] The children's visual acuity was assessed using the acuity card procedure and also by assessing the finest grating that could elicit a pupillary response. Whereas a behavioral response to a patterned stimulus can be detected at birth,[88] the pupil response to a grating stimulus does not develop until 4 weeks after term. The pupil response to a patterned stimulus is thought to be a measure of cortical activity.[89] Cocker *et al.* found that, in children with DVM, there is delayed development of the behavioral and pupillary response to gratings. Based on these observations, Cocker *et al.* suggested that DVM affects a segment of the visual pathway common to both the acuity card and pupil grating response.[62]

Some authors have proposed that the existence of two visual systems may explain DVM.[90] A subcortical, extrageniculostriate system was thought to be responsible for vision in the first few months of life before the geniculostraite system matures. This concept was supported by the observations of Dubowitz that lesions near the thalamus were more likely to affect visual behavior than lesions in the visual cortex.[37] Young infants were thought to be dependent on subcortical pathways (extrageniculostriate visual system) for visual function with cortical visual functions developing later. There are descriptions of visual function in premature infants with cortical lesions being similar to infants with no such lesions, but infants with subcortical lesions display abnormal visual function.[91] Cortical function is also believed to be responsible for binocular visual responses and smooth eye movement, both of which develop at around 6–8 weeks. This is the time of visual attentiveness of normal infants but is delayed in DVM.

Cortical function matures between 3 and 5 months of age, thus coinciding with the period when DVM often improves.[92] The similar recovery pattern seen in patients with DVM suggests a common process. Cocker *et al.* investigated the contribution of the cortical and subcortical visual systems in infants by assessing preferential looking and pupillary responses to pattern stimuli.[62] Preferential looking can be elicited from birth and is thought to be mediated by subcortical pathways, whereas the response to

pattern stimuli cannot be detected before 4 weeks and is thought to be mediated by cortical pathways. Interestingly, Cocker found delayed development of both responses suggesting involvement of both cortical and subcortical systems in DVM.[62]

Retina

In the normal infant, maturation of the macula continues following birth with central retinal cones taking at least 14 months to reach adult dimensions.[93] However, flash ERG studies in children with DVM show normal age-adjusted responses and suggest that the retina is functionally mature at birth.[16] Therefore, DVM is not likely to be due to immaturity of the retina.[5] Infants with DVM have a dense visual deficit, one that cannot be accounted for by delayed foveal development.

Optic nerve

Beauvieux was first to suggest that DVM might be due to a delay in myelination of the visual pathways.[3] The infants he studied had a black discoloration of the optic discs. In 1947, Beauvieux noted the optic disc in some children with DVM appeared slate gray but became normal as vision improved.[3] A delay in myelination of the optic nerve was considered a likely cause of DVM. However, children with DVM have normal pupillary responses and tend to improve between 3 and 5 months of age. Myelination of the distal optic nerve continues up to 2 years of age.[20] The latency of pattern evoked VEPs reaches adult levels by 3–5 months and is not significantly different between infants with DVM and age-matched controls.[23] Delayed myelination of the posterior visual pathways has also been implicated in DVM; however, in most cases, MRI shows age-appropriate myelination.[94] Visual recovery occurs too rapidly to be due to myelination of the visual pathway.

Saccadic eye movements

Another hypothesis is that eye movement abnormalities (apraxia) may be misinterpreted as poor vision. The assessment of visual behavior in infants is to a large degree interpreted based on visually directed ocular movements. The assessment of visual acuity in children often relies on accurate fixing and following however normal fixing and following relies on saccadic and pursuit functions as well as visual acuity. To perform well in preferential looking tests, it is necessary for the patient to generate adequate saccades. The apparently inattentive child should have saccadic function tested to distinguish a saccadic palsy. By definition, children with DVM have normal saccadic function.[60] Tressider *et al.* found that infants with DVM had severely reduced visual acuities when assessed by Teller forced-choice preferential looking.[59] In contrast, patients with DVM have normal VEPs when compared to age-matched controls. Harris *et al.* considered whether an abnormality of saccades might be responsible for apparent visual inattention in these children.[60,75] Infants with poor visual behavior should have an assessment of their saccadic function and VOR. The VOR should be normal; however, a lack of the fast phase of the VOR has been reported in some normal preterm infants.[61] The assessment of saccades is crucial to help differentiate DVM from a global saccadic palsy or ocular motor apraxia. Brainstem saccadic dysfunction does not appear to be the cause of DVM as infants with DVM have been shown to have normal binocular full-field optokinetic nystagmus.[66]

Cortex

Another requirement of good visual behavior is visual attention. Hoyt had suggested that there is no evidence for failure of any primary visual system and that temporary visual inattention is the cause of apparent poor vision.[2] Dubowitz found that thalamic lesions had a greater effect on visual function in infants than lesions of the visual cortex.[91] This was thought to be because the subcortical system was responsible for early visual function; however, this may also reflect an abnormality of visual attention. Harris *et al.* proposed that apparently poor vision in children with DVM is due to difficulty in distinguishing objects from their background perhaps due to an abnormality in the parietal cortex.[60] This is perhaps due to a disorder of higher cortical function and the visual association areas. Harris *et al.* were unable to elicit saccades or visual tracking to visual objects, but there was a normal full-field rapid build-up OKN response.[60] The normal OKN response was only present when the infant was viewing binocularly or during monocular stimulation in the temporonasal direction. There was almost no monocular OKN in the nasotemporal direction. Harris concluded that infants with DVM are delayed in orientating to local regions of the visual field, perhaps due to delayed development of the extrastriate cortical structures.[60] Children with DVM may have an abnormality of figure-ground separation or attentional pathways. The normal OKN suggests normal brainstem function, the normal pattern VEP, and normal retinogeniculostriate pathway.

The observation that children with DVM have age appropriate VEPs and ERGs strongly suggests that DVM is not a disorder of the macula or visual pathways. It is more likely that DVM is caused by a problem with the visual association areas. It seems most likely that DVM is due to an abnormality in the attention-inattention mechanism. We, therefore, support the idea that Beauviuex's original term, temporary visual inattention, more aptly describes this condition and should be adopted in place of DVM.[2] When we are presented with several objects in our visual field, they compete for neural representation. The visual network consists of a "bottom-up" stimulus driven process and a "top-down" executive function to detect the stimulus of attention. Functional MRI studies have shown that the bottom-up system depends on the frontal eye fields, globus pallidus, caudate, and putamen.[95] The top-down response is also controlled in areas outside the visual cortex, namely, the parietal cortex, superior colliculus, and pulvinar.[96] In infants, lesions of the thalamus have a greater impact on visual function than lesions of the visual cortex.[91] This is probably because lesions in the thalamus affect visual attention mechanisms.

Summary of pathophysiology

The evidence suggests that infants with DVM have normally functioning retina, optic nerves, visual cortex, and saccades. The

etiology of DVM is unknown but is perhaps multifactorial. For example, DVM has been observed in infants whose mothers use cocaine, perhaps secondary to a neurotransmitter imbalance.[80] A recent update of DVM by Russell-Eggitt *et al.* summarizes that DVM is likely to represent a spectrum of neurological abnormalities with multifocal involvement of most probably parietal cortical function.[66] However, most of the current studies have been relatively small retrospective case series. There have been two prospective studies, namely, by Lambert *et al.* and Tresidder *et al.* which will be discussed further.[56,59] Despite the findings of Lambert *et al.*, many studies have found children with DVM to have abnormal VEPs. Russell-Eggitt *et al.* had suggested that this may be because DVM has more than one cause.[66] Children who have had neonatal periventricular hemorrhages have been shown to have immature and delayed VEP waveforms compared to normal premature children. Perhaps, some infants with DVM have had unrecognized periventricular hemorrhages. A perinatal insult may affect the visual association areas and attentional mechanisms. The most likely cause of DVM is a disorder of visual attention mechanisms.[67]

Conclusion

Delayed maturation of vision is a diagnosis of exclusion and retrospection, the exact etiology of which is unknown. Most children with DVM will present to the ophthalmologist during the first 12 weeks of life with concerns about reduced visual awareness. Visual maturation may be considered the process of development of adult levels of visual acuity or the attainment of maximal visual potential for an individual (own definition). Opinions vary as to whether the term DVM should only apply to those infants who display such visual behavior and who have normal systemic and ocular examinations or whether it may be associated with other ocular or non-ocular abnormalities. The creation of a classification system for DVM aids our understanding of the condition and may help when counseling parents regarding their child's prognosis. Children with different types of DVM show different recovery patterns and have different long-term prognoses. Electrodiagnostic testing (ERG and flash and pattern VEPs) may also help predict the visual prognosis and exclude other causes of visual inattention. Unfortunately, the interpretation of VEPs requires large numbers of healthy age-matched controls, something that is difficult to achieve in most centers. The heterogeneity of DVM and the difficulty in comparison between electrodiagnostic tests in different centers means comparison between studies of children with DVM is also difficult. DVM is a retrospective diagnosis, but it is characterized by absolute visual inattentiveness and a rapid recovery, often over 2–3 days. Newer techniques such as functional neuroimaging may provide further understanding to the etiology of DVM.

Method of Literature Search

Papers and abstracts relevant to DVM were identified by a MEDLINE literature search covering the years 1980–2018 and included articles published in the English language. Search terms included DVM, delayed visual development, dissociated visual development, and visual developmental delay. Additional sources were identified from references in the appropriate articles.[97,98]

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