

DEVELOPMENT OF A QUANTITATIVE METHOD TO MEASURE VISION IN CHILDREN WITH CHRONIC CORTICAL VISUAL IMPAIRMENT*

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ABSTRACT

Purpose: Cortical visual impairment (CVI) is the most common cause of bilateral vision impairment in children in Western countries. Better quantitative tools for measuring vision are needed to assess these children, to allow measurement of their visual deficit, and to monitor their response to treatment and rehabilitation. The author performed a series of experiments to assess the use of the sweep visual evoked potential (VEP) as a quantitative tool for measuring vision in CVI.

Methods: The first experiment was a reliability measure (test/retest) of VEP grating acuity thresholds of 23 children with CVI. To validate the VEP procedure, VEP grating acuity was compared to a clinical measure of vision, the Huo scale, and to a psychophysical measure of vision, the Teller Acuity Card procedure. Finally, the sweep VEP was tested as a tool for defining optimal luminance conditions for grating acuity in 13 children with CVI, by measuring grating thresholds under 2 different luminance conditions: 50 and 100 candela per square meter (cd/m^2).

Results: Retest thresholds were similar to original thresholds ($r^2 = 0.662$; $P = .003$, 1-tailed t test). Grating VEP measures correlate significantly with the clinical index ($r^2 = 0.63$; $P = .00004$). Teller acuity measurements are also similar to VEP measures in children ($r^2 = 0.64$; $P = .0005$) but show lower acuities compared to the VEP for children with particularly low vision. Finally, 3 of 13 children tested under 2 background luminance conditions showed paradoxical improvement in grating threshold with dimmer luminance.

Conclusions: The sweep VEP tool is a reliable and valid means for measuring grating acuity in children with CVI. The tool also shows promise as a means of determining the optimal visual environment for children with CVI.

Tr Am Ophth Soc 2001;99:253-269

INTRODUCTION

The leading cause of bilateral vision impairment in children in Western countries is cortical visual impairment (CVI).^{1,2} This surprising finding, which reflects a change in the epidemiology of childhood vision impairment, stems from better outcomes in the management of some pediatric eye diseases (eg, congenital cataracts) as well as higher survival rates of children with perinatal hypoxia and ischemia (ie, preterm infants with damage to the central nervous system). CVI is caused by bilateral cerebral damage, either to the optic radiations or visual cortex, resulting in deficits in bilateral central visual acuity. This disorder typically occurs perinatally and is often of long duration, hence the need for better quantitative methods to assess vision in this population of preverbal children. Such methods, which are currently not available, could be used to determine the level of visual disability and the severity of the injury as well as to monitor rehabilitation in

children with CVI. *The goal of this study is to establish a quantitative method for measuring vision in children with CVI, based on the hypothesis that the sweep visual evoked potential (VEP) is a reliable and valid method in this approach.*

The sweep VEP was chosen as a possible tool for quantitative measurements of vision in children with CVI because it offers certain advantages. First, no verbal response from the patient is required to make the measurement. Second, a motor response in the form of head movement or eye movement to view the visual stimulus is also not necessary.

The sweep VEP is an untested method of studying children with CVI. To test the author's hypothesis, the *reliability* of the sweep VEP was first determined by using a grating stimulus in a repeat examination of a group of children with CVI. Second, the *validity* of the sweep VEP was tested by correlating the results of grating acuity measures in this patient population with (1) a clinical index and (2) Teller grating acuity measures (a behavioral test). Finally, this study also investigates the potential value of the sweep VEP in delineating a visual rehabilitation program for children with CVI. Specifically, grating acuity was measured under different lighting conditions

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(luminance) to determine whether a specific lighting condition(s) might improve visual function in some children. The hypothesis of this particular experiment is that certain children may be better managed (literally, may see better) in an environment with favorable lighting conditions.

Included in the following section is a clear definition of CVI, a discussion of the clinical findings related to this condition, evidence supporting CVI as an important cause of bilateral visual impairment in children, and a description of the underlying causes of CVI. Because the prognosis for visual development or recovery in CVI is variable, it becomes essential to establish an effective rehabilitation program. This section will serve as a preamble to the study, in which different background luminances were used to measure vision in children with CVI. The methods and results of this work will be presented after reviewing earlier neuroimaging, VEP, and behavioral measures of vision for CVI. The present study shows that the sweep VEP is a reliable and valid method of studying vision deficits in children with brain damage. Furthermore, the sweep VEP may be useful in defining a rehabilitation strategy for children with vision loss caused by central nervous system injury.

CORTICAL VISUAL IMPAIRMENT: BACKGROUND INFORMATION

DEFINITION AND TERMINOLOGY

Cortical visual impairment is a neurologic impairment defined as bilateral loss of central vision (visual acuity) caused by damage to the central nervous system. In other words, visual acuity is reduced as a result of nonocular disease.^{3,4} CVI occasionally coexists with other eye abnormalities, for example, in certain neurodegenerative disorders that affect the retina and central nervous system (eg, adrenoleukodystrophy). Strictly speaking, CVI manifests as impaired visual acuity with normal pupillary reaction bilaterally and a normal outcome on ophthalmologic examination.

In some cases, CVI is an acute reaction to a reversible disease process, such as transient CVI associated with head trauma. These cases rarely come to the attention of the ophthalmologist because symptoms and signs recede after a few hours or days. The research presented in this study concerns the condition known as *chronic CVI*.

Certain terms are sometimes used synonymously with CVI. *Cortical blindness* is the term initially coined by Marquis in 1933 to describe patients with visual loss but normal pupillary reactions.⁵ While this diagnostic term is still used for adults with loss of vision due to central nervous system injury, its use for children is not recommended because the term *blindness* implies total loss of vision.

One of the remarkable aspects of CVI is the near universal retention of residual vision, a phenomenon that explains many of the diagnostic features of CVI, discussed below. In fact, children with CVI are rarely ever completely blind. The term *cerebral blindness or impairment* is preferred by some investigators, because the term encompasses a wide range of etiologies that may affect gray matter *and* white matter.⁶⁻¹⁰ *Nonocular visual impairment* also is used by some,¹¹ but this term is confusing because ocular impairment may occur simultaneously with cortical impairment, particularly in children.

In summary, the term *cerebral visual impairment* is arguably more accurate in defining children with visual impairment caused by neurologic injury, but *cortical visual impairment* is so entrenched in the literature that it is preferred. In fact, vision impairment due to white matter disease (eg, periventricular leukomalacia) will invariably also affect the visual cortex directly or indirectly, lending accuracy to the term CVI.

The possibility that a broader range of visual impairments could be added to the general CVI category has also been addressed in recent years.⁹ In CVI, visual acuity is decreased because areas subserving macular function have been damaged. The macula is subserved by as much as two thirds of the visual cortex,^{12,13} so loss of visual acuity is very likely to accompany any injury to this part of the brain. Yet there are many other types of visual function that may be damaged without affecting visual acuity. Prosopagnosia, the inability to recognize faces, occasionally occurs in children in the absence of loss of visual acuity.¹⁴ Simultagnosia occurs after bilateral superior occipital lobe injuries, resulting in the inability to focus on more than 1 visual object at a time.¹⁵ In cerebral akinetopsia, afflicted individuals cannot perceive moving objects.¹⁵ In all these cases, visual acuity may be normal, despite the presence of a vision abnormality. Dutton¹⁵ recently proposed that these visual disturbances be termed *cortical visual dysfunction* (CVD). Certain children with CVI may show signs of CVD, but typical cases of CVD (those without acuity loss) should not be grouped with CVI. The term *cortical visual impairment* in this context will therefore be reserved for visual impairment in children with associated reduced visual acuity.

A spectrum of other related disorders is also arguably due to associated visual cortex damage. Learning disabilities including dyslexia are sometimes attributed to cortical visual damage. Again, in this paper we will adhere to the strict definition of CVI, which must include loss of visual acuity associated with neurologic damage.

PHYSICAL FINDINGS

The clinical examination is usually sufficient to establish the diagnosis of CVI. Children affected by CVI, who have

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no anterior visual pathway abnormality, will have a normal eye examination but show poor visual behavior. For example, they will fail to regard a face or to pay visual attention to their surroundings. The ophthalmoscopic examination in typical cases of CVI is normal. Some children will have both anterior visual pathway disease *and* CVI. In these cases, clinical judgment is used to determine whether a component of vision impairment is caused by CVI. Additional physical findings may help to clarify the diagnosis and must be taken into account in determining the overall management of the child with CVI.

Children with CVI may experience head and eye movement difficulties.¹⁶ Abnormalities such as apraxia of eye movement and gaze palsies are common and pose potential problems in diagnosis of CVI. Pursuit eye movement problems are very common in CVI and can also be problematic for affected children. In these ocular motor disturbances, it may be difficult to distinguish the true loss of visual acuity from a disorder of eye movement that may mimic vision impairment. In fact, one benefit of developing a quantitative tool to measure vision in CVI would be the ability to distinguish true acuity loss from eye movement disorders mimicking vision loss in nonverbal children.

Visual field defects are also common in CVI.^{10,17} Measurement of visual field defects is difficult, even in normal children.^{18,19} A type of confrontation device has been used effectively to measure visual fields by so-called confrontational examination, which relies on the child's eye or head movement to indicate that a target has been observed. With severe cases of CVI, where motor control is poor, measurement of visual field may be particularly difficult.

The blink response to threat is not useful in the diagnosis of visual disability. The response to threat is a learned behavior, not present until the age of 3 months. Children with CVI develop this response at an even later age, which complicates any interpretation of the response.

Behavioral Findings in Cortical Visual Impairment

A constellation of complex behavioral changes is known to occur in CVI, and these are particularly noteworthy because they probably are adaptations to an underlying visual impairment problem.²⁰ The first of these is slow, inefficient, and highly variable visual performance. CVI patients characteristically have a short visual attention span.^{5,16,21,22} They typically see better in familiar surroundings^{5,23} and when they are relaxed and well rested. This variable visual efficiency, with better visual behavior noted at some times, could challenge the accurate and meaningful measurement of vision. If reliable, quantitative visual acuity measures could be obtained, then other aspects of behavior associated with vision could account for this variation in visual behavior (eg, poor motor control mimicking

vision impairment or "subclinical seizures" interfering with visual behavior).

Color vision and perception of movement are often preserved in patients with CVI, a finding which sometimes leads to the construction of visual stimuli (eg, optotypes) in color, rather than in black and white, to enhance the vision of children with CVI.²³⁻²⁶ Red and yellow are frequently cited as preferred colors for CVI patients.^{16,24} In the experiments reported here, children with CVI were asked to view black and white stimuli, but future studies using color stimuli could also help to guide rehabilitation efforts for CVI.

Often, CVI patients use peripheral vision to search for objects. They may turn their heads before reaching for an object (retinal reach),^{3,5} with the head turned away from the side affected by vision loss. It has been hypothesized that this behavior is due to a desire to use peripheral vision,^{5,27} or perhaps to allow time to assimilate and process visual information. People with visual impairment often bring objects closer to their eyes to increase linear magnification of the object of visual interest. CVI patients also display this behavior, although they may do so to simplify their field of view by excluding extraneous visual information and reducing the "crowding" effect.^{16,21} This effect occurs when flanking visual targets inhibit a person's ability to see the foveal target (ie, the visual target of interest).

Gazing at lights is a common feature in patients with CVI²⁸ and provides the basis for one aspect of this study. Some patients with CVI flick their fingers in front of the light source, or blink excessively, or gaze at flickering fires, or stare at spinning fans.²⁸ Paradoxically, a third of CVI patients exhibit photophobia²⁶ but still gaze at lights from time to time. Children tend to outgrow their photophobic behavior. If a test were devised to determine the specific lighting condition that would permit enhanced vision in different subgroups of children with CVI, it could provide important information on the optimal visual environment for a visual rehabilitation program. For example, the child who fares better in reduced lighting conditions might see better and learn faster in an environment with reduced background luminance.

EPIDEMIOLOGY OF VISUAL IMPAIRMENT IN CHILDREN

In the past, conditions such as congenital cataracts and retinopathy of prematurity were usually responsible for bilateral low vision in children. These conditions are now more easily treated with advanced microsurgical instruments in the case of cataracts and with cryotherapy or laser therapy for retinopathy of prematurity. Hence, CVI has emerged as a major cause of visual impairment in children,^{21,24} particularly in developed countries,³ where new treatment options have extended to these other eye diseases. (Not included in this section is a discussion of

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unilateral vision impairment commonly observed in amblyopia, for example.)

The incidence of CVI is increasing.²³ In a study of 5 Nordic countries, Rosenberg and colleagues²⁹ noted that brain damage accounts for a growing number of cases of childhood visual impairment. The investigators implicated improved medical care since critically ill children are now more likely to survive with increasingly severe medical problems. CVI per se is not life-threatening, although the neurologic abnormalities associated with CVI may have been fatal in the past. In Chile, 2.1% of blind children or those with severe visual impairment, who are enrolled in schools for the blind, can attribute their visual difficulties to CVI.³⁰ This finding is an underestimate, however, because students with higher functioning skills are generally enrolled in schools for the blind; also, many children were too young for formal education at the time of the study. Rogers³¹ investigated visual impairment in Liverpool. CVI was the most common diagnosis (49% of the study population) among children with both visual impairment and additional neurologic disability. The Oxford Register of Early Childhood Impairments² reports the overall incidence of bilateral vision impairment at 0.5%, with 29.5% of the cases due to CVI. The second leading cause of vision impairment in this register is nystagmus, at 14.1%. In Northern California, CVI is the leading cause of visual impairment in children under the age of 5 years.¹

The overall incidence of bilateral vision impairment in children in Western countries is probably 0.5%.² If a third of these cases are due to CVI, then this disorder will affect more than 1 in 1,000 children, making CVI an important cause of vision impairment in this population. CVI usually occurs in conjunction with other serious neurologic abnormalities, such as seizures and motor deficits.³² There is no known treatment. In fact, no satisfactory method exists for quantifying visual deficit in these children. To establish a successful treatment or rehabilitation regimen, it is important to establish a method to evaluate the effectiveness of the treatment modality.

ETIOLOGY OF CORTICAL VISUAL IMPAIRMENT

Disorders of the human visual system can be divided into at least 2 categories: those that affect the anterior visual pathways and those that affect retrogeniculate or posterior pathways (optic radiations and visual cortex). A third potential category encompasses the large array of conditions where the child's visual perception is altered (eg, CVD). This classification scheme is useful because diseases that affect bilateral anterior, as opposed to retrogeniculate, visual pathways produce different clinical findings. In this section, we review diseases and etiologies that affect the visual cortex and associative cortical areas. For

a child to suffer impaired visual acuity from a central nervous system injury, the injury must be bilateral. Unilateral injury affecting the optic radiations or visual cortex will cause a hemianopia without loss of visual acuity.

Hypoxia/Ischemia

The most common cause of CVI is a hypoxic/ischemic injury,^{3,21,24,33-35} usually in the perinatal period. Events such as placental insufficiency, dystopia, and asphyxia from many causes are usually responsible for insufficient oxygenation in the infant's brain. At least 60% of children with neonatal hypoxic/ischemic encephalopathy have cerebral visual impairment.⁹ In one study of children who sustained perinatal hypoxia, *all* subjects had some form of visual impairment.¹⁷ The pattern of neurologic damage varies depending on whether the injury occurs in a preterm infant or in a term (or postterm) infant. A third pattern of injury is seen in full-term infants with profound asphyxia, as discussed below.

Hypoxia (lack of oxygen) or ischemia (tissue death due to loss of blood flow and, thus, oxygen deprivation) in the preterm baby leads to a characteristic injury of the brain, namely periventricular leukomalacia (PVL).^{25,36} The mechanism and distribution of injury in the preterm infant are predicated on the location of the watershed zone, which is in the germinal matrix, adjacent to the ventricles and in close proximity to the optic radiations. PVL can be detected by a number of methods, including magnetic resonance imaging (MRI), in which the affected tissue around the ventricles of the brain appears white owing to loss of fluid and increased density of tissue. In serious cases of PVL, cysts may form in the affected tissue.⁸ Such cystic change, particularly in the posterior part of the brain (as opposed to periventricularly located cysts), is associated with a poor neurologic and visual prognosis.^{8,11,25}

In term or near-term infants, hypoxia/ischemia causes injury to the brain, in the distribution of the cerebral arteries and in their watershed zones. Germinal matrix vessels have regressed by 32 weeks' gestation, so that periventricular white matter is usually spared. The prognosis for recovery of vision is probably better when the injury involves the striate cortex, not the optic radiations;³⁷ term infants usually experience direct damage to the striate from hypoxia/ischemia.

In cases of severe asphyxia in term infants (eg, caused by prolonged cardiac arrest; severe abruptio; severe, prolonged hypotension), damage occurs chiefly in the basal ganglia and hippocampus. Involvement of basal ganglia on neuroimaging indicates a particularly poor developmental and visual prognosis.³⁸ Basal ganglia disorders are almost invariably accompanied by generalized involuntary movements involving the head, neck, and eyes, which interfere with motor functions and vision.³⁹

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Focal infarction (stroke) is also a possible effect of perinatal hypoxia and ischemia. Mercuri and colleagues⁴⁰ report that the left hemisphere, particularly in the area of the middle cerebral artery, is susceptible to focal infarction in the perinatal period, although a bilateral insult is required for the development of CVI.

Shunt Failure

Transtentorial herniation can lead to compression of the posterior cerebral arteries against the tentorial edge.³³ This can lead to ischemia and occipital lobe infarction. The neurologic damage is more severe if there is a rapid onset, as more gradual compression allows the vascular system to compensate.³³

Epilepsy

Wong²² reported a poor prognosis when the cause of "cortical blindness" was status epilepticus. Fortunately, status epilepticus is now rare. Chen and associates⁴¹ also suggest that epilepsy is associated with a poorer prognosis. CVI is very common in infants with infantile spasms, especially when the electroencephalogram (EEG) is hypsarrhythmic. The abnormal visual function can result from loss of visual acuity and impaired perception. While the etiology of infantile spasms is often unclear, the cause of the profound visual inattentiveness is the same brain disturbance that results in seizures and in abnormal EEG patterns.

Infections

Bacterial meningitis,²⁴ encephalitis,⁵ and meningitis/encephalitis²¹ may cause CVI. Bacterial meningitis is associated with a poorer prognosis than other causes of CVI.⁴¹ Congenital toxoplasmosis can also cause CVI, as may neonatal herpes simplex.³³

Drugs or Poisons

Antenatal use of cocaine and amphetamines will occasionally cause CVI.³² The presumed mechanism of injury is damage to developing or already developed central nervous system vessels caused by vasoactive substances, resulting in infarction of key neurologic structures.

Metabolic Disease

Most of the neurodegenerative disorders have the potential to disrupt cortical vision. It is unlikely that children will present with the isolated finding of CVI. One exception is the case of adrenoleukodystrophy, which may show prominent visual manifestations early in its course.^{42,43}

Complications of Cardiac Treatment

CVI has been reported in children after cardiac arrest and open heart surgery.^{24,44} Wong²² reported a poor prognosis when the cause of "cortical blindness" was cardiac arrest.

Trauma

Head injury is a major cause of CVI,²¹ with half of the trauma cases the result of battering (ie, child abuse). Trauma-induced CVI is frequently described as transient and is often accompanied by headaches, confusion, and vomiting.⁴⁵ Children may be especially prone to such injury because of flexible skulls, relatively less cerebral-spinal fluid volume, and a relatively reduced distance between cortex and cranium, compared with adults. Cranial injury may induce transient ischemia or edema.^{44,45} Vasospasm is more likely to occur in children than in adults and may cause hypoxia in the occipital cortex owing to its location between the 3 major cerebral arteries. There may be some link between transient posttraumatic CVI and migraine headaches. Posttraumatic visual problems may lead to complete blindness.⁴⁴

Twin Pregnancy

There have been reports in the literature implicating twin pregnancy as a cause of CVI.^{24,46} Monochorionic twins are particularly vulnerable, presumably due to twin-to-twin transfusions. Ironically, the larger twin is usually more adversely affected because of its expanded blood volume and resulting vascular stress. Clinicians should investigate the possibility of a twin pregnancy when faced with a child with neurologic damage or CVI.

Central Nervous System Developmental Defects

Central nervous system developmental defects may be associated with CVI.⁴¹ Examples include lissencephaly, holoprosencephaly, and schizencephaly. At least some of these disorders may also be associated with optic nerve hypoplasia, occasionally making the distinction between CVI and anterior visual pathway visual deficits difficult.

ASSOCIATED NEUROLOGIC AND OPHTHALMOLOGIC DEFICITS

Neurologic disorders are frequently seen in association with CVI. Whiting and associates⁵ reported that all subjects in their study had associated neurologic deficits: abnormal mental development, cerebral palsy, seizures, microcephaly, hydrocephalus, sensorineural hearing loss, myelomeningocele, and progressive CNS degeneration. In fact, chronic CVI is virtually always associated with other serious neurologic abnormalities.^{21,22,31,32,47}

Chronic CVI is also associated with ophthalmologic abnormalities, including various types of nystagmus, strabismus, and refractive error.^{21,48} Optic nerve atrophy, which itself causes vision impairment, has been seen in patients with CVI³⁹ and will cause the diagnosis of CVI to be uncertain in some cases. Clinical judgment is used to distinguish anterior pathway disease from CVI in these cases, because there is no precise test to determine the

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relative contribution of optic atrophy or CVI to the overall vision impairment of a given child. While strabismus, nystagmus, and refractive errors are not diagnostic of CVI, they are also often present in patients with CVI³² and should be corrected (eg, with glasses) to maximize residual vision.²¹ Since hypoxic/ischemic insults are often the cause of CVI, other visual deficits also could be caused by the same initial insult. Visual field development may be delayed in premature children who suffer perinatal hypoxia/ischemia. Strabismus with a cerebral origin may also occur in these children.⁸

PROGNOSIS

Most patients with CVI do not regain normal vision.¹⁷ However, improvement is usually seen.^{3,17,21,32} Visual improvement may be sudden, particularly in cases of traumatic injury; more typically, visual recovery is gradual. Very little is known about specific prognostic findings in CVI. However, many researchers state that children with CVI have a poor prognosis when they display extensive motor involvement, severe seizures, and low intellectual functioning.^{23,32,37} In other words, children with CVI and extensive neurologic damage have the least favorable prognosis for recovery of vision. The finding of periventricular leukomalacia confers a particularly poor prognosis,³⁷ compared to damage to the visual cortex per se.

TOOLS FOR MEASURING THE VISUAL DEFICIT IN CORTICAL VISUAL IMPAIRMENT

Quantitative information about a patient's condition can be clinically useful and comforting to patients and their families. A variety of techniques can be used to assess the extent of injury to the posterior visual pathways, but while a particular technique may be a good predictor of prognosis in experimental cohorts, in the case of individuals, such predictions are less useful.^{10,25} Clinical assessment must be performed in conjunction with brain imaging studies.

FORCED CHOICE PREFERENTIAL LOOKING

In forced choice preferential looking (FPL), an observer located behind a screen presents a series of cards with different grating lines to the child. A grating card is displayed on one side of the child's visual field, while a luminance-matched blank field is displayed on the other side. When children see the grating card, they usually will look at it. The observer notes the child's eye movements without knowing on which side the grating card appeared, and acuity is determined by noting the finest grating to which the child reliably orients his or her gaze (Teller Acuity Procedure). Inattention or inability to direct gaze could prevent a child from following a stimulus above chance

levels.⁴⁸ Moreover, FPL measures may be difficult to interpret in children with head and eye movement difficulties. Thus, failure to reliably direct gaze toward a grating card may be partly determined by motor coordination problems in the child with CVI. On the other hand, FPL testing may reveal specific defects in gaze control in conjunction with other tests.

ELECTROENCEPHALOGRAM

The VEP provides general information about geniculocalcarine dysfunction and occipital responses to photic stimuli.²⁴ The EEG can be interpreted in association with VEPs. The presence of normal alpha rhythm, superimposed on a normal background, rules out cortical visual impairment and homonymous hemianopia due to cortical lesions.²⁷ Reactive alpha rhythm is a good prognostic finding in CVI.²⁷ Recently, alpha reactivity has been successfully applied to the study of patients who have misrouting of visual pathways, such as occurs in albinism.⁴⁹ The study of alpha rhythm may therefore have application to visual disturbances that cause hemispheric visual system asymmetries.

NEUROIMAGING

Neuroimaging of the brain can be used to confirm the clinical diagnosis of CVI.²³ Magnetic resonance imaging is often used to detect PVL in the first days of life, although the child's visual outcome cannot be accurately predicted on the basis of neuroimaging findings.⁸ MRI is also used to assess asphyxia in neonates⁵⁰ and may be a better predictor of outcome in the first week following injury. A normal MRI scan correlates with normal vision, although an abnormal MRI finding does not necessarily indicate loss of visual acuity.⁵¹ MRI scans can be used to detect delayed myelination, which can be caused by perinatal hypoxia,⁵¹ and are more reliable in the detection of damage to the optic radiations than to the visual cortex.¹⁰ Finally, the MRI scan may show selective damage to periventricular white matter, with a less favorable prognosis for visual recovery.^{38,51}

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

The single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are used to investigate changes in cerebral blood flow.⁵² These tools may be better at predicting outcome than MRI scans but have not been widely used, mainly because PET requires delivery of a small amount of a radioactive isotope.

ULTRASOUND

Ultrasound, which is portable and noninvasive, is often used to detect PVL in the first days of life and may be

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more sensitive than MRI during this period. In most cases, ultrasonography is performed transfrontally.⁵³ Eken and colleagues⁷ found that ultrasound could be used to correlate structural abnormalities with visual outcome.

FUNCTIONAL MAGNETIC RESONANCE IMAGING

Functional magnetic resonance imaging (fMRI) shows promise as a diagnostic tool. The fMRI demonstrates areas of the brain that are metabolically active. However, fMRI requires an alert, immobile, cooperative patient and, therefore, has limited use in children.

VISUAL EVOKED POTENTIALS

Research on VEPs has focused mainly on this method's usefulness in confirming CVI or on its prognostic value for visual outcome.⁵⁴ Several types of VEPs can be performed, including the transient, nonpatterned flash VEP and the transient pattern reversal VEP, each of which yields information about the temporal waveform of responses to single presentations of a visual stimulus. Clarke and colleagues¹¹ found that CVI patients with normal flash VEPs had a good prognosis for improvement. Flash VEP may not accurately assess higher levels of visual processing, however, pattern VEPs are more useful for monitoring visual development and rehabilitation in children.³⁵

Multichannel VEPs have been used to diagnose CVI. Ratios of activities between multiple recording electrodes in children with CVI can be calculated and compared mathematically to normal, control subjects. Children with CVI show low occipital to parietal activity, helping to confirm the diagnosis.⁵⁵

In the steady-state sweep VEP, a patterned stimulus is periodically temporally modulated (eg, at 2.5 Hz or above) while the pattern elements gradually change size. An evoked response is time-locked to the stimulus modulation, and the amplitude of the response varies with stimulus visibility, allowing visual thresholds to be quantitatively estimated.

Steady-state VEPs show promising potential for quantification of visual loss in CVI and offer the advantage of testing several types of visual function (eg, contrast sensitivity, grating acuity, vernier acuity).^{56,57} This is the type of VEP stimulus chosen for the set of experiments described in this thesis.

METHODS

SUBJECTS

The institutional review board approved this research project, which also conforms to the Helsinki criteria for human research. Written informed consent was obtained from the parents after the procedure had been carefully

explained to them. The subjects were a group of children recruited from the practice of the author or from the practice of other pediatric ophthalmologists in the region. In some cases, the Blind Babies Foundation of Northern California helped with further recruitment. The author reviewed the medical records of the patients.

The ages of the subjects at the time of enrollment in the study ranged from 6 months to 16 years, although most were younger than 3 years. All subjects had a clinical history consistent with an injury to the central nervous system, mostly due to perinatal hypoxia/ischemia. In most children, injury was sustained in a natal or perinatal event. A few children had developed encephalitis in the first year of life. CVI was diagnosed on the basis of poor visual attention or behavior associated with a normal ophthalmologic examination and normal pupillary responses. In almost all cases, the degree of vision impairment was considered clinically profound. Information on etiology, age at onset of CVI, age at test, and type of data (reliability) obtained is presented in Table I. Table II shows diagnosis, age at onset of CVI, and age at testing of different luminance conditions. When no threshold could be determined, this was recorded as "no" measurable threshold, and the data was included.

VEP grating acuity was measured in 23 subjects and then retested in the reliability phase of the experiment. Grating visual acuity was measured at least once with sweep VEP techniques in 41 children, while 21 consecutive children were assessed using the Teller Acuity Card procedure (see below). A clinical assessment (Huo scale rating) was determined for 29 of the children, and luminance comparisons for 13 children. Every effort was made to measure Huo criteria, Teller acuity, repeat thresholds, and luminance comparison thresholds in consecutive children. In some cases, however, children could not return because of intercurrent illness or other conflict.

STIMULI

Vertical sine-wave luminance gratings were created on the face of a 24 x 18-cm video monitor at a space average luminance of 100 cd/m² and a Michelson contrast of 80%. The gratings were generated by a raster graphics board (NuVistat) at a resolution of 1,536 x 480 pixels. Subjects were tested at a distance of 70 to 100 cm from the video monitor screen in a darkened examination room. They were given a fixation toy, consisting of a small piece of jewelry or animal model, but most were unable to attend to it. The proximity of the monitor screen to the subject's face helped to ensure fixation. The subject's visual attention was carefully assessed by direct observation.

Sweep VEP Stimulus and Measurements

For the VEP grating acuity measurements, a pattern onset-offset stimulus was displayed that modulated at a

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TABLE I: CLINICAL CHARACTERISTICS OF CHILDREN WITH CVI AND TYPE OF TESTS PERFORMED

PATIENT	AGE AT TEST	AGE AT CVI ONSET*	ETIOLOGY	RELIABILITY	TELLER	HUO
1	71 wk	Preterm (0)	HIE	X	X	X
2	2.7 yr	Perinatal (0)	HIE	X	X	
3	11 yr	Perinatal (0)	HIE	X	X	X
4	45 wk	Perinatal (0)	HIE	X	X	X
5	28 wk	Perinatal (0)	HIE	X		X
6	2.2 yr	Perinatal (0)	HIE	X	X	X
7	2.4 yr	Perinatal (0)	HIE	X		X
8	6.9 yr	Perinatal (0)	HIE	X		X
9	91 wk	Perinatal (0)	HIE	X		X
10	2.8 yr	Perinatal (0)	HIE	X	X	
11	5.9 yr	6 mo	Encephalitis	X	X	
12	70.9 wk	Perinatal (0)	HIE: Twin	X		
13	47 wk	Perinatal (0)	HIE: Twin	X		
14	2.2 yr	Perinatal (0)	HIE	X		X
15	100 wk	Perinatal (0)	HIE	X	X	
16	27.7 wk	Prenatal (0)	HIE	X	X	X
17	1.5 yr	Perinatal (0)	HIE	X		
18	2.5 yr	Perinatal (0)	HIE	X		X
19	46 wk	Perinatal (0)	HIE	X		
20	63 wk	Preterm (0)	HIE	X		
21	2.9 yr	4 mo	Trauma/auto accident	X	X	X
22	10 mo	Preterm (0)	HIE (ROP)	X		X
23	18 mo	Premature (0)	HIE	X		X
24	5.0 yr	Perinatal (0)	HIE		X	
25	4.0 yr	Perinatal (0)	Mitochondrial disease		X	X
26	15.6 wk	Perinatal (0)	Perinatal		X	X
27	4.5 yr	Perinatal (0)	HIE		X	X
28	2.8 yr	2 yr	HIE,cardiac arrest		X	X
29	4.7 yr	15 mo	Encephalitis		X	X
30	3.3 yr	5 mo	CVA		X	X
31	71.6 wk	Perinatal (0)	HIE		X	
32	4.8 yr	Perinatal (0)	Trisomy 13/encephalocele		X	X
33	9.0 yr	Perinatal (0)	HIE		X	X
34	3 mo	Perinatal (0)	HIE		X	
35	9.9 yr	Perinatal (0)	HIE			X
36	15.9 wk	Perinatal (0)	HIE			X
37	97 wk	Preterm (0)	HIE (shaken)			X
38	4.0 yr	5 mo	Meningitis			X
39	60.1 wk	4 mo	Near SIDS			X
40	3.0 yr	Perinatal (0)	HIE			X
41	5.0 yr	Perinatal (0)	HIE			X

CVA, cerebrovascular accident; CVI, cortical visual impairment; HIE, hypoxic/ischemic encephalopathy; ROP, retinopathy of prematurity; SIDS, sudden infant death syndrome; reliability, test-retest.

*Zero indicates age at onset to be birth.

frequency of 5 Hz. This temporal frequency was chosen on the basis of preliminary pilot data in children with CVI³⁷ and to avoid frequencies that might induce seizure activity in susceptible children. Subjects were tested in a consistently dimly lit room, usually sitting on a parent's lap or in a wheelchair, with head and torso immobilized.

Each threshold was measured using the swept parameter technique. The grating stimulus was presented over 10 equally spaced, linear steps from above threshold to below threshold. Threshold was determined for each trial by extrapolating the VEP response to zero. Threshold

measures from multiple (at least 10) 10-second trials were averaged for each testing condition. The grating was set at 1 to 3 cycles/degree (cpd), depending on the subject (ie, those with better visual fixation were started at higher acuities) and then swept to a spatial frequency of 10 to 20 cpd, again depending on the subject. For example, those children with higher grating acuities were tested from 3 to 20 cpd. When threshold measures could not be determined, "no measurable grating threshold" was recorded in the data, and the trial was repeated in the retesting phase of the experiment (Fig 1).

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TABLE II: CLINICAL CHARACTERISTICS AND ADDITIONAL TESTING OF CHILDREN WITH CVI UNDERGOING VEP GRATING ACUITY ANALYSIS UNDER 2 LUMINANCE CONDITIONS

PATIENT*	AGE AT TEST	AGE AT CVI ONSET†	DIAGNOSIS
1 (4)	45 wk	Perinatal (0)	HIE
2 (5)	28 wk	Perinatal (0)	
3 (11)	5.9 yr	6 mo	Encephalitis
4 (36)	15.9 wk	Perinatal (0)	HIE
5 (28)	2.8 yr	2 yr	HIE, cardiac arrest
6 (new)	6.0 yr	4 mo	Meningitis
7 (12)	70.9 wk	Perinatal (0)	HIE: Twin
8 (13)	47.0 wk	Perinatal (0)	HIE: Twin
9 (31)	71.6 wk	Perinatal (0)	HIE
10 (15)	100 wk	Perinatal (0)	HIE
11 (23)	18 mo	Premature	HIE
12 (33)	9.0 yr	Perinatal (0)	HIE
13 (new)	18 mo	Perinatal (0)	HIE

CVI, cortical visual impairment; HIE, hypoxic/ischemic encephalopathy; VEP, visual evoked potential.

*Number in parenthesis indicates patient number when tested under Table I.

†Zero indicates age at onset to be birth.

Children with neurologic disease could have reduced VEP responses on account of seizures, anticonvulsants, poor accommodation, nystagmus, and roving eye movements. Careful monitoring of visual fixation helped to obviate some of these issues, as did signal averaging across many trials. We had no means to monitor accommodation in these experiments.

An EEG was also performed during the experiment to check for intercurrent seizure activity and to monitor background noise. A few of the children experienced an underlying seizure disorder during testing, and the experiment was interrupted for a few minutes and then resumed. No child suffered a grand mal convulsion during the study, nor were there any other clinical complications. For the retest phase of the experiment, subjects returned

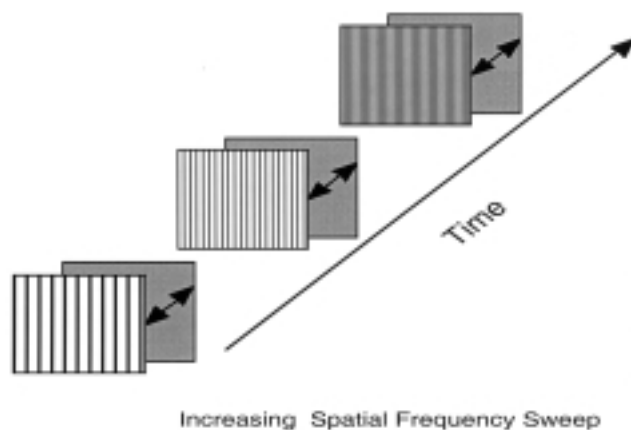


FIGURE 1
The sweep visual evoked potential grating stimulus.

on a different day for a second testing session under similar experimental conditions, usually 1 to 3 months after the first session. In a few cases, retesting was delayed because the child had been ill and/or hospitalized.

Two different experimental conditions were chosen for the luminance-effect experiment, based on earlier work by Allen and colleagues,⁵⁸ which indicated that VEP grating thresholds peak above approximately 1 cd/m². The background luminance was therefore set at either 50 or 100 cd/m² (Fig 2), each of which should yield comparable grating thresholds. Grating thresholds were determined as already described and were evaluated by statistical analysis (see below).

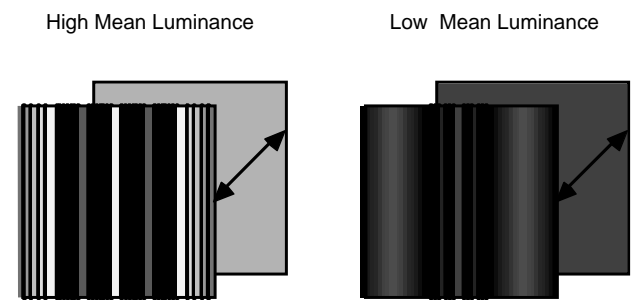


FIGURE 2
Comparison of luminance conditions in 13 subjects. Left, high luminance (100 cd/m²); right, low luminance (50 cd/m²).

Behavioral Procedure

Twenty-one children were also tested using the Teller Acuity Card procedure, which measures grating acuity according to behavioral responses to a visual stimulus.⁵⁹ A masked and well-trained observer administered the test at a distance of 1 m from the subject. The testing stimulus was presented in a room with no visual distractions. The subject's response to the stimulus was assessed by the observer and recorded as the highest spatial frequency that the subject responded to reliably. In some cases, the subject's head and neck were stabilized to promote best performance. Because many of the children experienced motor problems, a white stage was not used as background in this part of the study.

COMPARISON TO HUO CRITERIA OF CLINICAL VISUAL BEHAVIOR

Twenty-nine children in the study were assigned a clinical score based on criteria established by Huo and colleagues⁶⁰ for clinical visual behavior. The score for each subject is derived from clinical observations recorded either in the author's practice or at the onset of the VEP experiment. Clinical scores were assigned without prior knowledge of the VEP threshold measure.

Huo's criteria are ranked from 1 to 6 according to the

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following scale that we modified for this study: (1) light perception only; (2) fixation on a face; (3) reliable fixation on small objects in the environment; (4) visual acuity 20/200 to 20/800, either actual or estimated; (5) visual acuity 20/50 to 20/200, either actual or estimated; and (6) normal visual acuity. The Huo score was then compared to the VEP threshold data. Estimations of measurable visual acuity (eg, 20/200) seldom had to be based on clinical judgement, which is potentially very unreliable. Most children in whom a Snellen acuity could be recorded were neurologically higher functioning and verbal.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Matlab software application. A 1-tailed *t* test of paired comparisons was run in 3 data sets, each containing acuity measurements taken under 2 different conditions: test versus retest, VEP versus Teller acuity data, and 50 cd/m² versus 100 cd/m². This test returns a significance level (*P*) indicating the probability that the mean difference between test acuity and retest acuity is zero.

The test-retest reliability measure was computed by using a type 2 regression analysis to determine if there is a significant level of correlation (ie, reliability) between the 2 conditions. Linear regression of these data resulted in a correlation coefficient whose significance is measured as a *P* value. This *P* value indicates the probability of obtaining this correlation coefficient from 2 totally uncorrelated sets of measurements.

Linear analysis was also run for the Teller-VEP data and the Huo-VEP data to determine whether a correlation exists between these measures of vision. The analysis was run on linear and logarithmically derived data sets to determine whether statistical significance could be derived from both types of data.

A type 2 regression analysis was also used to compare grating acuity to Huo criteria.

RESULTS

VEP GRATING ACUITY RESULTS

Figure 3 shows the range of VEP grating thresholds obtained for 41 children with CVI compared to results of normal control children. The figure shows that older children tend to demonstrate higher grating acuities, suggesting an improving developmental trend, since nearly all children had perinatal disease (ie, concurrent with onset of CVI: see discussion below). A wide range of acuities can be seen, although most children with CVI achieved VEP grating acuity measures below 10 cpd.

RELIABILITY TESTS OF VEP GRATING ACUITY

Test-retest reliability scores are shown graphically in

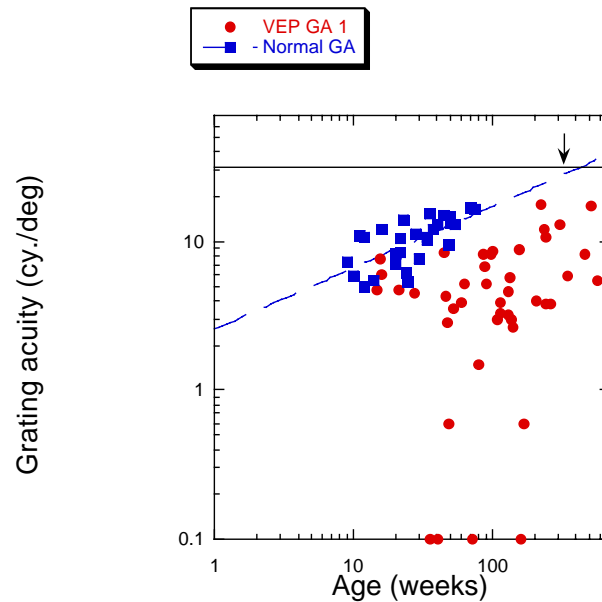


FIGURE 3

VEP grating acuity measures in all children tested. Results are compared to normative data from Skoczenski and Norcia.⁵⁶ Arrow points to line indicating normal, mature grating acuity. VEP grating acuity is presented on log scale. GA, grating acuity.

Fig 4. Twenty-three subjects were available for retesting, and the results in the second examination confirmed the reliability of the method; that is, the results of the second test were similar to those of the first, with one exception. The repeat examination was performed within 3 months of the initial examination, with few exceptions (illness pre-

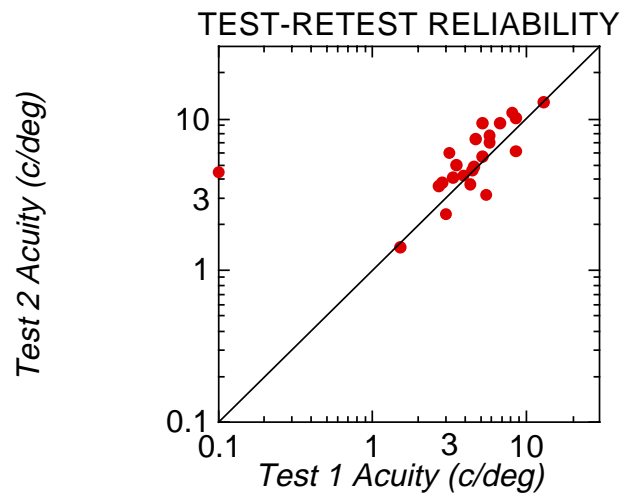


FIGURE 4

Test-retest results of 23 subjects. X axis represents first test, and Y axis shows results of retest. Linear regression model for these data yields the equation $y = 0.87x + 1.67$; $r^2 = 0.662$ ($P = .0003$). Standard errors (SE) on slope and intercept were 0.27 and 0.35, respectively. Note that most data points are above the line. This suggests improvement between first and second tests. A 1-tailed *t* test of paired comparisons is significant at the .048 level when calculated for log acuities and at the .006 level when calculated for linear acuities.

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cluded prompt follow-up).

Linear regression analysis of these data yielded $r^2 = 0.662$, which is significant at $P = .0003$ (1-tailed t test). The P value indicates the probability of obtaining this correlation coefficient from 2 totally uncorrelated measurements (ie, the test and the retest from each subject). Results of this test point to the likelihood that the test is highly reliable.

Most data points are above the exact reliability line, suggesting that some improvement in VEP grating acuity or in the ability to measure it occurs in a short time in children with CVI. A less likely explanation would be that children showed test improvement with practice. This is less likely because so many of the children were substantially intellectually impaired. When grating acuities are plotted logarithmically, a 1-tailed t test of paired comparisons yields a test-retest significance level at $P = .048$ (significant difference). Excluding left and right outliers, $P = .018$. Note that one data point on the graph is far from the cluster. Even including this point, as noted previously, P is significant at the .048 level.

When the same data points are compared on a linear scale, the 1-tailed t test yields $P = .006$. Excluding the 2 outliers, $P = .001$.

COMPARISON OF THE SWEEP VEP WITH PSYCHOPHYSICAL MEASUREMENT OF GRATING ACUITY

Figure 5 shows the results of a comparison study between VEP grating acuity and a psychophysical measure of grating acuity, the Teller Acuity procedure. In general, children showed lower acuities on the behavioral measure, compared to the electrophysiological (VEP) measure. In the high acuity range, a better approximation of the 2 types of tests was noted. Regression analysis of the data

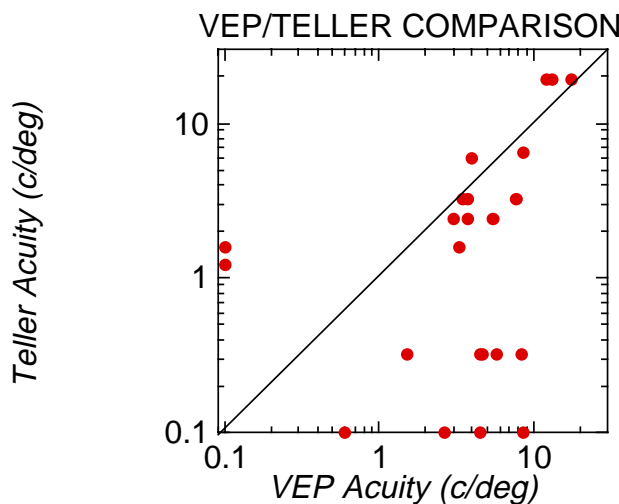


FIGURE 5

Results of Teller acuity compared to VEP grating acuity in the same subjects. Note better apparent correlation at higher acuities. The linear regression equation for these data is $y = 1.15x + 2.31$; $r^2 = 0.64$; $P = .0005$.

yields the linear equation $y = 1.15x + 2.31$; $r^2 = 0.64$; $P = .0005$, indicating a strong correlation between the 2 data sets. A 1-tailed t test of paired comparisons yields $P = .008$ for log acuities and $P = .035$ for linear acuities. This P value is the probability that the difference between the Teller acuity data and VEP data is 0 and demonstrates the likelihood that the data sets, while correlated with each other, are also different.

COMPARISON OF SWEEP VEP GRATING ACUITY AND A CLINICAL INDEX OF VISION (HUO CRITERIA)

A correlation was found between VEP thresholds for grating acuity and clinical findings (Fig 6). Most children had low (poor) clinical scores, and these correlated with low thresholds on the VEP tests. Regression analysis of these data yields the equation $y = 2.60x - 0.72$, with a correlation

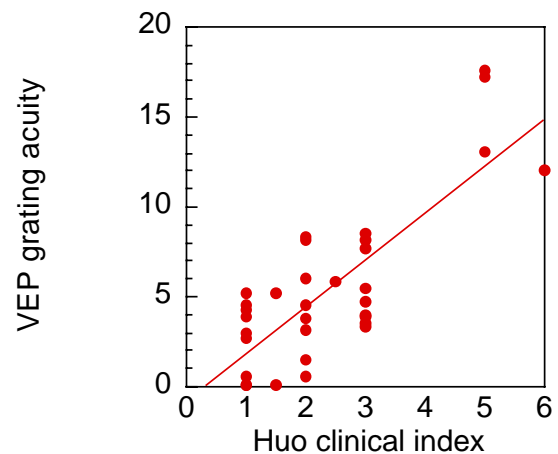


FIGURE 6

Huo clinical measurement compared to VEP acuity measurement. VEP grating acuity is validated by the clinical measurement (linear regression equation is $y = 2.60x - 0.72$; $r^2 = 0.63$; $P = .00004$).

coefficient of 0.63, which is significant at $P = .00004$. Regression of log VEP acuity versus Huo index generated a correlation coefficient of 0.33 with $P = .03$.

RESULTS OF LUMINANCE VARIATION

Figure 7 shows VEP grating thresholds for 13 subjects, taken at 50 and 100 cd/m^2 . Note that some subjects show unexpected improvement in dimmer luminance conditions (50 cd/m^2), while others show a decline in acuity in dimmer luminance. As would be expected, a number of children showed no effect.

DISCUSSION

The clinical measurement and assessment of vision in children with CVI is difficult and often inaccurate, for many reasons. The first of these is that children with CVI are usually preverbal because the neurologic injury has

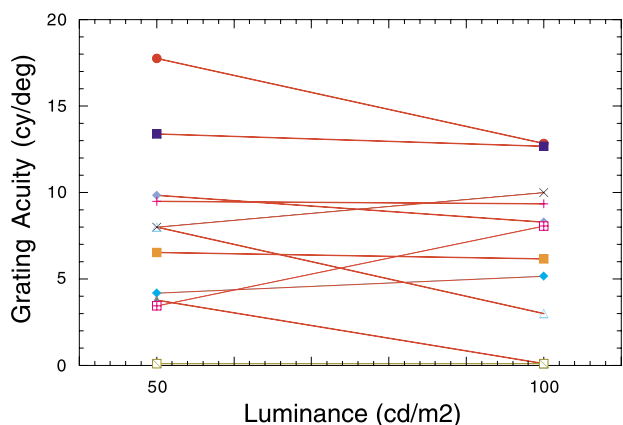


FIGURE 7

Results of testing of 13 children under 2 luminance conditions: 50 and 100 cd/m^2 . X axis shows the 2 conditions, and Y axis indicates linear grating acuity thresholds. Note that some children have lower, while others have higher, thresholds at 100 cd/m^2 , an unexpected finding. Three children had low grating acuities, and these did not vary between luminance conditions; thresholds for these children is not plotted. Children with normal vision would not be expected to show a difference between these conditions.

occurred in the perinatal period, or nonverbal because the injury has also caused widespread neurologic damage. Therefore, the clinician cannot expect reliable, verbal feedback from the patient affected by CVI. Furthermore, many children with CVI also have motor complications, including disturbances of ocular motor function. Some children with CVI are unable to make an appropriate eye, head, or neck movement to look at an object of visual interest in their environment, even though they may be able to "see" the object. This difficulty in motor control may complicate the interpretation of behavioral signs of vision in children with CVI (eg, psychophysical measurements of vision). Given the increasing incidence of CVI, there is a great need to establish quantitative measures to assess vision in this population of children.

In this study, the author tested the reliability of the sweep VEP for measuring grating acuity in children with CVI. Several strategies were employed to examine whether the measurements obtained with the sweep VEP actually reflect the underlying visual status of the child with cortical visual impairment. These tests, devised to validate the experimental procedure, suggest that the technique reliably reflects the underlying visual status of the child. The results obtained in this study show promise for the future implementation of this technique in the clinical setting. Finally, different lighting conditions were used in an attempt to determine the usefulness of the VEP technique in predicting a rational rehabilitation strategy. To this effect, grating acuity was measured under different luminance conditions to determine if children affected by CVI show their best visual performance in relatively dim or brightly lit surroundings.

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The choice of grating acuity as a VEP stimulus was based on the potential for comparison with a well-known behavioral measure of grating acuity, the Teller acuity procedure, and on the large amount of data from other studies examining Teller acuity in children. Grating acuity as measured using the Teller acuity procedure has been used to monitor and assess vision in other landmark studies of conditions that cause bilateral vision impairment (eg, retinopathy of prematurity).⁶¹⁻⁶³

Grating acuity has limitations. Grating acuity only roughly approximates optotype acuity and is probably subserved by different cortical mechanisms than those used for recognition acuity. In the future, other stimuli may offer a better reflection of optotype (Snellen) acuity. Vernier acuity threshold measurements show promise in this regard.^{64,65} Grating acuity thresholds were chosen for these experiments because there is more scientific experience measuring grating acuity in young and nonverbal children, particularly using preferential looking techniques.

The VEP technique in this study differs from techniques used in previous investigations of children with CVI. In this series of experiments, we used a swept stimulus pattern technique to measure a threshold for grating acuity. Other investigators have tested flash or pattern reversal VEP.^{11,35} The sweep VEP requires multiple trials but records a threshold and provides additional data on signal-to-noise ratios. The VEP stimulus can be varied to adjust to the individual patient tested and can measure thresholds under a number of different stimulus conditions. In this set of experiments, we measured grating thresholds, but vernier acuity, contrast, and luminance thresholds can also be recorded.

The VEP was chosen as an experimental tool for several reasons. Children with CVI have a predilection to look at light, and so it was hoped that a luminescent stimulus source (the monitor) might attract the child's attention.^{26,27} CVI is usually accompanied by significant motor deficits. These deficits may preclude a motor movement to regard an object or stimulus of visual interest. Although studies of forced preferential looking can be performed on this group of children, they may be hampered by this motor deficit. With the VEP stimulus, a child can be positioned directly in front of the monitor, so that the stimulus subtends a wide angle of the subject's visual field. The child's head and neck can be stabilized whenever necessary to prevent inadvertent motor movements away from the stimulus. Other advantages and disadvantages of the VEP will now be discussed vis-à-vis the results of the various experiments.

MEASUREMENT OF GRATING ACUITY IN A LARGE COHORT OF CHILDREN WITH CVI

In all, 41 subjects with CVI had at least 1 session during

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which a VEP grating threshold was determined (Fig 3). Results are compared to a well-established historical control group,⁵⁶ also measured on the same stimulus and equipment. Grating thresholds are lower in children with CVI than in normal controls. The results also suggest a trend toward improvement with increasing age, although caution is indicated in interpreting developmental trends in these cross-sectional data. The data could also simply demonstrate a spectrum of static vision impairment in a heterogeneous population of children. Favoring the view that developmental improvement in grating thresholds occurs in this cohort is the finding that second tests of acuity in the reliability experiment were usually better, and to a statistically significant degree, than first tests.

The ability to obtain these data in a large cohort adds further evidence that the sweep VEP tool may be a useful technique for measuring children with CVI. One criticism of the VEP technique is difficulty applying it to children in the age range from 18 months to 4 years. In this cohort, we were successful in obtaining data across a broad age spectrum.

Another criticism of the technique is difficulty measuring sweep VEP thresholds in children with neurologic disease (see below). Such children may have brain malformations, roving eye movements, seizure activity, or depressed cortical activity caused by anticonvulsants. In these experiments, we coped with these problems by averaging the VEP signal across many trials and by carefully monitoring visual fixation. Nevertheless, our threshold results could have been uniformly depressed as a result of these problems. The reliability of our results offers some reassurance that this was not usually the case.

RELIABILITY OF VEP GRATING THRESHOLD MEASUREMENTS IN CHILDREN WITH CVI

Can a VEP grating threshold measure be reproduced reliably in the same child with CVI? Common arguments against the use of the VEP for clinical measurement stem from the concern that at any given time, the VEP threshold measurement could be variable (reliability), or that the VEP measure is not a reflection of the underlying disease or disease severity (validity). This cohort of patients with severe neurologic disability and a wide spectrum of vision impairment, ranging from light perception only vision to visual acuity of 20/50, is arguably the most difficult in which to assess vision. Problems encountered in measuring vision in these children included convulsive episodes during the test procedure; variable concentration caused by convulsions, anticonvulsants, or underlying severe central nervous system damage; motor impairment making it necessary to immobilize the child's head and/or torso so as to be able to direct the child's gaze to the stimulus; poor attention, particularly in the higher-functioning

children; and unpredictable illness in members of the cohort, making appointments problematic at times.

Signal averaging across many trials helped to obviate some of these problems. The VEP apparatus allows the tester to stop the trial and restart the same trial when fixation on the screen is lost, or when seizure activity or motion interferes with the test. Nevertheless, testing in some of the children was difficult, and it is possible that the VEP underestimated or poorly estimated acuity at least in some of the cohort. Structural brain abnormalities also could interfere with signal measurements and could cause the sweep VEP to measure acuity incorrectly.

Other investigators have encountered problems using the sweep VEP to measure acuity thresholds in children. In normal children, pooled data from subjects tested and retested show good reliability, but there is variability for each subject.⁶⁶ The sweep VEP may be useful for neurologically or developmentally impaired children, but inconsistent scores still occur.⁶⁷ Infants tested in different behavioral states may show variation in performance when tested with the VEP.⁶⁸ There is also evidence that certain anticonvulsants can interfere with VEP measurements.⁶⁹ For these reasons, results from these experiments should be viewed as preliminary.

The sweep VEP has been shown to be a reliable test in application to a normal cohort.⁷⁰ In this experiment, the author has demonstrated that it is usually reliable in a population with cortical visual loss, despite the potential problems noted above. Only one subject could not reliably repeat the test, because he was significantly neurologically obtunded at the second examination. Factors that may enhance the reliability of the sweep VEP include signal averaging across multiple, 10-second trials, the use of a luminescent stimulus source, and the fact that the test does not always require motor/behavioral responses as a prerequisite to measuring vision.

COMPARISON OF SWEEP VEP RESULTS TO A CLINICAL MEASURE OF VISION

Most of the subjects in this cohort had not attained any language milestones. In normal, preverbal children, (normal) visual acuity is inferred on the basis of normal pupillary responses, good visual fixation, normal anatomy, and the absence of nystagmus, strabismus, or refractive errors. All these factors were also normal in the cohort with CVI, except visual fixation. A clinical system was therefore devised that takes into account fixation and behavior.⁶⁰ In previous work,⁶⁰ these Huo criteria were used to monitor improvement in a large population of children with CVI. However, the criteria are very difficult to apply and, admittedly, an approximation of vision in children with CVI. The approximate nature of clinical assessment is the very problem necessitating a better, quantitative measure

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of vision in children with CVI.

Nevertheless, as one means of validating the VEP grating acuity data, it seemed prudent to compare the VEP thresholds to a clinical measure. The VEP measures would be suspect if they bore no relationship to the clinical status of the child. A strong correlation between clinical signs and electrophysiologic measures was found when thresholds were compared from children in whom a masked clinical assessment was obtained.

COMPARISON OF VEP GRATING THRESHOLD MEASURES TO FORCED CHOICE PREFERENTIAL LOOKING MEASURES

Another clinical measure of vision is forced choice preferential looking. In this test, a child is confronted with a blank card on one side and a grating card on the other. A threshold can be measured by testing the subject with increasingly difficult-to-see stimuli, until the child cannot see the grating card and thereby fails to make an eye movement to notice the card. The Teller acuity procedure has become a widely accepted means of measuring grating acuity in preverbal children. The test has been shown to be reliable and can be validated against clinical findings, both in normal subjects and in children with a variety of diseases.

However, FPL, of which Teller acuity is an example, could have limitations in the study of CVI. Its application to children with poor motor control is potentially problematic, because a motor movement is required to demonstrate visual perception. Despite the fact that FPL correlates with visual outcome in studies of another important cause of blindness in children, retinopathy of prematurity,⁶¹⁻⁶³ the FPL measures are sometimes not as sensitive as desired; that is, a normal or near-normal FPL result in an infant may only approximate Snellen visual acuity.

The Teller acuity card procedure offers a well-standardized means for comparison of VEP data. Figure 5 shows this comparison of 21 children with CVI. The graph shows that the VEP acuities were consistently higher, particularly in children with poorer vision. In children with better vision, a better correlation can be seen between Teller grating acuity and VEP grating acuity.

Results of this comparison should be interpreted cautiously. It is possible that fatigue in performance could be a greater factor when the Teller procedure is performed after the VEP, since FPL requires a motor response to a visual stimulus. Even so, the 2 measures, Teller acuity and VEP acuity, can be shown to correlate with each other, further validating the VEP as a potentially useful clinical and research tool.

One interpretation of the data is that behavioral testing underestimates vision in children with poor motor control. In support of this is the observation that

higher-functioning children showed FPL results more consistent with VEP results. Higher-functioning children are much more likely to be ambulatory and to have better neck, torso, and eye movement control. In the author's view, it is unlikely that the VEP overestimates vision in lower-functioning children, although this is also another interpretation. It is likely that the VEP measures grating acuity in children who cannot demonstrate the motor behavior linked to vision.

EFFECT OF LUMINANCE ON VEP GRATING ACUITY

Important clinical observations could be tested using the VEP system. Children with CVI show behaviors that have not been fully explained or confirmed quantitatively. One seemingly paradoxical behavior was measured: light attraction seen in some children with CVI and photophobia seen in others. The author tested the hypothesis that variations in illuminance of a grating stimulus will alter the grating threshold in some children with CVI.

Normal infants and adults have been studied at varying retinal illuminations. Dobson and colleagues⁷¹ used a behavioral technique (FPL) to measure grating acuity in 2-month-old infants and adults at a wide range of luminances. They found that adults and infants reach a peak threshold at the same luminance, which in their study was approximately 44 TD, corresponding to approximately 10 cd/m². Brown and colleagues⁷² arrived at similar conclusions in a study performed in 1987. In a similar study using the VEP, Allen and associates⁵⁸ found that grating acuity thresholds peaked above about one cd/m². Below the luminance level of approximately one cd/m², there is a decremental increase (worsening) in grating threshold as luminance decreases.

Given the results of these past experiments, 2 conditions were chosen for this study: 50 and 100 cd/m². If children with CVI behaved comparably to normal subjects reported by these other groups, there should be no significant difference in grating thresholds at the 2 different luminance levels. Taken as individuals, some children see better, some see worse, and others show no change with brighter illumination. The number of subjects makes statistical analysis of the data problematic. Furthermore, it is likely, on the basis of clinical histories, that these subjects are a heterogeneous group, some with better visual function and some with worse in dim luminance conditions.

One possibility to explain the variation in acuities seen is that the subject's accommodation or pupil size is affected by the different stimulus conditions, as it is well known that accommodation is erratic in infants.^{73,74} However, the change in pupil size would not alter the luminance effect enough to affect grating thresholds. Even so, the result should be that brighter illumination would increase (worsen) grating thresholds. There is

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nothing about varying luminance per se that should affect accommodative response. Another issue could be that these particular subjects are simply unreliable, showing varying threshold responses at different times. This also is unlikely (see above discussion of reliability).

Spatial resolution, particularly at high spatial frequencies, is mediated by a number of factors, including photoreceptor spacing⁷⁵ and optics of the visual system under investigation.^{76,77} In children with brain damage and poor vision, any mechanistic explanation of variations in grating acuity with luminance must evoke postphotoreceptor, central nervous system processes. In this regard, central photophobia has been described in adults as a result of thalamic stroke, the so-called thalamic glare syndrome.⁷⁸ The thalamus plays an important role in modulating afferent central nervous system input. Damage to the thalamus is known to occur in severe cases of perinatal hypoxia/ischemia. A thalamic injury mechanism still may not explain improved acuity seen in some children under conditions of diminished illuminance, unless the effect of luminance variation is exaggerated considerably at the postreceptor, higher-order neuron level.

Perhaps some other mechanism can explain the reason children with CVI are often drawn to look at brightly illuminated objects. This illuminance study seems to confirm this clinical finding: some of the children studied showed improved grating thresholds under brighter illumination. This finding is also unexpected, given previous studies' findings on the stability of grating acuity across a wide range of luminance conditions. It is also important to note the observation that some children showed the expected finding, no change in acuity as luminance varies. This additional observation points to the potential value of quantitatively analyzing the child's response to a different luminance condition.

Although a plausible mechanistic explanation for improvement under bright or dim luminance is lacking, this finding still has potential clinical significance. Predicting the child's optimal visual environment may go a long way toward maximizing a rehabilitation program tailored to the individual. If a child sees better at reduced luminance, for example, his or her teachers would be well advised to consider this as they present the child with visual learning tasks.

These series of experiments have shown that the sweep VEP is a reliable and valid tool for measuring vision in children with CVI. Furthermore, the tool may be used to help define a rehabilitation program for individual children. The VEP tool still has its limitations. It is complicated and requires 2 people to run effectively. VEP measurements are time-consuming as well. It is hard to imagine the sweep VEP as an office procedure in the near future.

On the other hand, time spent with children and their

families was invaluable. And, since most children showed some quantifiable grating acuity, confirming parents' perceptions and often contradicting reports from schools or family physicians, the impact on the families was usually very positive.

Future investigations in this laboratory will focus on expanding the use of the sweep VEP to measure vernier acuity in children with CVI and on endeavoring to develop VEP measures of cognition, since it is often not known whether children with CVI understand what they see.

CONCLUSIONS

1. Children with CVI show a spectrum of grating acuity impairment that can be measured using the sweep VEP technique.
2. The sweep VEP measures grating acuity in a reliable fashion.
3. When compared to a clinical measure of vision, the Huo scale, the VEP threshold measurement is valid and approximates clinical findings.
4. Compared to the Teller acuity procedure, the VEP appears to also be a sensitive index of vision. Teller acuity may underestimate grating acuity in CVI in some children. An alternative hypothesis is that VEP grating acuity overestimates grating acuity in some children. The VEP technique correlates significantly with the Teller acuity procedure, further validating the VEP technique.
5. The VEP tool may be useful for defining a rehabilitation program for visually impaired children. When children were tested under different luminance conditions, they showed an unexpected range of grating acuities, depending on the individual child.

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