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Vision assessments and interventions for infants 0-2 years at high risk for Cerebral Palsy: a systematic review

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Abstract

We performed a systematic review and evaluated the level of evidence of vision interventions and assessments for infants at high-risk for or with a diagnosis of cerebral palsy from 0-2 years of age.

Articles were evaluated based on the level of methodological quality, evidence, and clinical utilization.

Thirty publications of vision assessments and 5 of vision interventions met criteria for inclusion. Assessments included standard care neuroimaging, electrophysiology, neuro-ophthalmologic examination techniques that are utilized clinically with any pre-verbal or non-verbal pediatric patient.

The overall level of evidence of interventions was strong for neuroprotective interventions such as caffeine and hypothermia but weak for surgery, visual training or developmental programs.

There are few evidence-based interventions and assessments that address cerebral/cortical visual impairment-related needs of infants and toddlers at high risk for or with CP. Recommendation guidelines include the use of 3 types of standard care methodologies and 2 types of protective interventions.

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Introduction

The wide spectrum of sensory disturbances associated with cerebral palsy (CP) is attributed to lesions of the developing fetal or infant brain.(1) Early detection of CP is recommended through repeated neurologic assessments, behavioral observations, and neuroimaging studies, to refer for evidence-based services and minimize future activity limitations.(2,3) The vision problems of children with CP reflect the interactions between perinatal brain lesions and the early environment, with alterations of visual function resulting from experience-expectant and experience-dependent cortical processes. In children with CP, strabismus, refractive anomalies, optic atrophy, nystagmus, ptosis and accommodative dysfunctions are frequent. Neurological vision loss also called cerebral/cortical visual impairment, (CVI) (4,5) can result from visual neural processing dysfunctions commonly co-occurring with CP, rather than any defined ocular lesion.(6)

Despite a high incidence of visual impairments in individuals with CP, few prospective studies have focused on assessments and rehabilitation specifically targeting infants with or at high risk of CP under two years of age. Instead, a large body of clinical literature and retrospective studies documents the use of ophthalmologic, neuroimaging, and electrophysiological assessments to characterize vision in infants at risk for neurodevelopmental disorders. An aggregate and systematic review of these studies can provide insights on possible effective assessment for infants with CP. Similarly, systematically reviewing interventions aimed at improving visual function in this population may complement other early identification and rehabilitation approaches. Therefore, using validated assessment tools, we aimed to summarize the current literature on vision assessments and interventions for infants under 24 months at high-risk or with CP, and only with CVI.

Method

This systematic review includes literature about vision assessments and interventions including randomized controlled trials and other evidence-based studies representing the current level of evidence.

Search Strategy

This review included search of relevant terms in online research databases. Searches were performed between August and October 2016, and repeated again in March 2017 to evaluate the literature of vision interventions for infants aged zero to two years with or at high risk for CP.

To inform the evidence base supporting the application of early assessments and interventions for infants zero to two with or at high risk for CP, PubMed, Cochrane Library, MEDLINE, SCOPUS (EMBASE), CINAHL, and grey literature were searched (see Supplemental 1).

Inclusion criteria

Peer reviewed publications of interventions addressing vision assessments and rehabilitation interventions with infants at high risk for or with a diagnosis of CP were included when any of the study participants were under two years corrected age. Grey literature including dissertations, as well as publications in languages other than English were included.

Exclusion Criteria

Articles were excluded if they were not peer-reviewed publications, if they were letters, editorials, notes, caregiver questionnaires, or qualitative data-only reports.

Types of assessments

The clinical tools designed for the assessment of visual function or visual anatomy that are utilized with children at high risk or with a diagnosis of CP were included. The assessments categories were divided into electrophysiology, neuroimaging and behavioral.

Types of interventions

Interventions provided by medical providers, licensed therapists/professionals or caregivers/parents trained by therapists/professionals were included. Vision-specific training interventions as well as interventions which target visual impairment as secondary outcomes (e.g. neuroprotection) were identified and included.

Types of participants

The recommendations contained in this guideline apply to infants at high risk for CP(7) or with a diagnosis of CP, aged zero to two, as well as those with CVI.

Data Review and Quality Appraisal

Two independent reviewers performed the searches of all databases and search terms. Article abstracts were compiled and reviewed to determine applicability to the current review. Selected articles were retained and reviewed by an additional independent reviewer to confirm inclusion/exclusion criteria. Included articles were then reviewed in full-text independently by three reviewers. Assessment publications reporting instruments specifically designed for infants at high risk or with a diagnosis of CP were evaluated with a checklist of Consensus-based Standards for the selection of health Measurement Instruments (COSMIN).(8) It is a 4-point scale that evaluates psychometric properties including reliability, validity, responsiveness, and interpretability of assessment tools.

Intervention publications review followed the guidelines of the International Clinical Guideline for Cerebral Palsy search terms and was performed in accordance with the principles of A Measurement Tool to Assess Systematic Reviews (AMSTAR)(9), the Grading of Recommendations Assessment, Development and Evaluation (GRADE)(10), and the Cochrane Collaboration's tool(11) for assessing risk of bias in randomized trials.

Results

A total of 290 assessments and 282 interventions records were identified in the initial terms searches. After each search, duplicates, presentation materials, and qualitative data - only reports were excluded. Flow diagrams of study selections in PRISMA format are presented in Figures 1 and 2.

Assessments

Twenty-nine articles met the inclusion criteria. One report included information about design of assessments specifically for infants with CP and therefore met criteria for evaluation with COSMIN (Table 1). Twenty-eight included clinical care neuro/ophthalmologic, neurophysiological and neuroimaging assessments (Table 2). The age of initial or follow-up assessments ranged between preterm and 19 years. Of the 29, 16 were prospective observations, and 13 retrospective. Study size ranged from n=11 to n=164.

Interventions

Out of 282 articles meeting search criteria, 6 articles met inclusion criteria (Table 3). These included 2 vision-specific interventions studies in infants with CP and 4 publications on neuroprotective interventions targeting visual impairment as secondary outcomes in infants at high-risk for CP. Two studies were systematic reviews (Table 4), 2 were randomized controlled trials (Table 5), 1 was an observational, cross-sectional, prospective study and 1 was a case series review. The studies included infants and toddlers with multiple developmental delays or disorders from 0-2 years. Study size ranged from n=50 to n=1640.

Discussion

Section I: Assessments

Neuroimaging—While early studies utilized cranial ultrasound and CT scans to help identify infants more likely to have CVI, MRI has been the clinical tool of choice to study the structural integrity of visual pathways. Structural abnormalities of the occipital cortex and optic radiations, as visualized on T1 and T2- weighted sequences, is associated with abnormal visual functions in infants with brain damage, including periventricular leukomalacia, brain hemorrhage and neonatal encephalopathy.(5,23,31) Basal ganglia involvement in infants with neonatal encephalopathy, and thalamic atrophy in those with periventricular leukomalacia, are strong predictors of abnormal visual function. In cortical visual loss, exotropia and a normal optic disc appearance are more common, while in subcortical visual loss esotropia, and optic nerve hypoplasia are reported.(17) More advanced MRI techniques can be also useful.(31,34) MRI diffusion imaging offers a quantitative evaluation of the integrity of the optic radiations, by means of fractional anisotropy values, which is highly correlated with visual function scores in preterm born infants at term.(14) Also, the extent of activation of the occipital cortex on functional MRI in infants with periventricular leukomalacia is directly correlated with visual acuity.(39)

Neurophysiology—Visual evoked potential (VEP) methodology allows quantitative measurement of visual responses in the macular region (not the periphery), even in infants

and preverbal children as no behavioral response is required. Flash-VEP testing presents simple bimodal stimuli to assess patients with severely impaired vision.(19) Reactivity to eye closure can be evaluated in the EEG stream by quantifying the occurrence, symmetry and frequency of spikes occurring above delta wave-baseline patterns in open-eyed wakefulness (which also depend on maturity). (15) Steady state VEPs, such as those measured in orientation reversal paradigms a measure of visual function development and cortical maturation.(26) Sweep VEPs can determine contrast thresholds and visual acuity in less severely affected infants, by modulating the frequency of the sweep patterns.(25)

Behavioral Assessments—Abnormalities of visual function identified through behavioral assessments are common in infants with or at high risk for CP, and may include poor visual acuity, reduction in visual fields, disorders of eye-movement, strabismus and complex visual-perceptual defects. Descriptions of frequently used behavioral vision assessments follow. **Optokinetic nystagmus (OKN)** is an involuntary motor reflex responsible for the ability to follow a moving object while keeping a steady gaze. Testing is performed by rotating a striped drum, black and white patterned board or mirror. The distance between the infant and the drum at cessation of the reflex response is recorded. **Visual field** assessment in infants is performed using confrontation techniques, during which an examiner attracts the infant's attention centrally. An assistant introduces another object into the periphery, and the examiner determines if the infant orients to the peripherally presented object, estimating the visual arc. A variant of this, kinetic perimetry, utilizes two white spheres as the objects. **Oculomotor function assessments** evaluate the presence of expected or atypical eye movements such as light gazing, light fixation, gaze fixation, and tracking. **Visual acuity** of cooperative infants without severe CVI can be assessed using preferential looking towards patterned cards (Teller, Keeler, Cardiff, Griffiths, Berkley and variations). Acuity is measured in cycles per degree, and recorded as the threshold of the smallest width of the grating on presented cards that elicit a typical response as referenced to normative data.(46,47) Visual acuity can also be tested using optotypes in children as young as 3 years, but none are designed for infants under 2 years.

Only one assessment battery met criteria for evaluation using COSMIN and had been previously been included in a published systematic review of older children and adolescents. (48) The CVI range is an assessment of visual function, partially validated in a doctoral dissertation. While its reliability and discriminative validity as relates to functional levels in CP and responsiveness to interventions may yet be studied in the future, the CVI range currently has only internal consistency, and limited aspects of content validity (see Table 1). Therefore, as it relates specifically to visual function impairments of infants under 2 years with or at high risk for CP, there is currently not enough evidence to make a recommendation regarding the use of the CVI range.

Recommendations: Our recommendations are to use the standard care clinical visual function examinations available for infants. While these tools have been validated with typically developing populations, they are also useful in characterizing deficits in infants with CP. No evidence to date indicates that they are not applicable to the CP population although items 1 and 3 may be more challenging in patients with disabilities.

1. MRI and diffusion weighted imaging are recommended to evaluate the integrity of the optic nerve, optic radiations, visual cortex and other structures involved in cerebral/cortical visual function.
2. VEPs are particularly recommended for measurement of macular visual function, maturation, acuity and contrast threshold as they do not require active participation of the infants.
3. A battery of behavioral assessments is recommended in cooperative and less impaired infants to evaluate OKN, visual fields, acuity and oculomotor function.

Section II: Interventions

Neuroprotective interventions for vision—Most neuroprotective interventions in populations of infants at high risk for CP aim to improve neurodevelopmental outcomes in the broadest sense, by decreasing the occurrence of neurosensory impairments. Some of these interventions have proven more effective than others in specifically improving vision.

In a Cochrane Review updated in 2013 (41) infants with moderate to severe neonatal encephalopathy at high risk for CP had a non-significant reduction in blindness after receiving hypothermia as compared to a non-cooled control group (typical RR 0.62 (95% CI 0.38 to 1.01), typical RD -0.04 (95% CI -0.08 to 0.00) as supported by 7 studies (749 infants). Another systematic review had similar conclusions but no calculated effect sizes. (45) In a large multicenter RCT infants treated with caffeine scored an average 3.5 points higher in the visual perception domain on the Beery-Buktenica Developmental Test than those who were not treated (OR 3.2 (CI 1.2 to 5.2) $p=0.001$). (44) In a large RCT (43) 2 /191 preterm infants treated with recombinant erythropoietin (rhEPO) had severe visual impairment vs. 0/174 in the placebo control group (OR -0.01, CI (-0.02 to 0.04) $p=0.5$). Notably, infants in this study received rhEPO in a dose of 3000 IU/kg, three times within the first 42 hours after birth, a dosing schedule not common to all current rhEPO trials.

Surgical correction of esotropia and exotropia—In an observational study of 50 children with CP, (40) the relationship between severity of CP, timing of surgery and alignment and binocular fusion was examined. In this cohort, the duration of esotropia/exotropia in children who achieved optimal alignment and in those who did not was 2.6 ± 1.2 years vs. 4.8 ± 2.6 years ($p < 0.05$). Similarly, the duration of esotropia/exotropia in children who gained versus those who did not gain a grade of fusion was 2.2 ± 0.9 years vs. 5.1 ± 3.7 years ($p = 0.02$). Of the children with CP, 46% ($n = 23$) gained at least one grade of binocularity after one or more surgeries. Independent of CP severity, 58% of the children had good alignment after surgery. Fifty percent of children with mild CP who had improved binocularity gained sensory fusion (i.e., Worth or Polaroid four-dot) versus 19% in those with severe CP. A gain of stereopsis (> 3000 arc seconds) was achieved in 25% with mild CP. Children with mild CP had two-to-threefold greater chance of gaining Worth/Polaroid four-dot fusion or stereopsis than those with more severe CP

Visual training for cerebral impairment—An observational study of 78 infants aged 7 months to 4 years, included 15 infants with CP and 30 of which had received at least one

course of rehabilitation (two 4-week cycles of training with black-and-white slide exposures, black light training and multisensory stimulation).(42) After training 20/30 infants (66.6%) had increased attention and spontaneous visual curiosity and required less marked conditions of contrast and light for daily interactions than at baseline. Six children (20%) who had the most severe neuromotor damage, had no change after treatment.

Other related intervention research and expert opinion—There is a paucity of interventions aimed specifically at improving visual function in infants at high-risk or with CP. Expert opinion mainly focuses on rehabilitative interventions for infants with CVI, in whom parent-guided activities for integration of vision with other sensory experiences may amplify visual information and/or compensate for severely impaired vision((49),(23) (45)). The underlying mechanism for success of interventions for infants with CVI is purported in most literature on the topic to be promotion of an infant's emotional/relational development through the support of the parent-infant relationship. In support of this concept, in Optimum VI, a novel clinical trial for infants with severe or profound visual impairment, guided parent-focussed journaling of visual impairments is evaluated as a possible adjunct to community-based early intervention programs. (50) The Early Support Developmental Journal for babies and children with visual impairment has activity cards and guides parents through the progression of their child with visual impairment's development.(51)

Recommendations

1. For infants with a history of moderate to severe encephalopathy, hypothermia is strongly recommended to decrease risk of CVI, with benefits clearly outweighing the risks.
2. For very preterm infants, caffeine is strongly recommended to increase visual perception, with benefits also clearly outweighing risks. For very preterm infants, recombinant human erythropoietin is not recommended to decrease the risk of severe visual impairment, although the recommendation is weak.
3. Based on two studies and expert opinion in the field, the following very weak recommendations can be made, meaning that alternative approaches are likely to be better for some patients under some circumstances. Surgical correction of esotropia (bilateral medial rectus recession) and exotropia (bilateral lateral rectus recession) may be beneficial in children with CP when it is performed to approximate surgery schedules for typically developing children, with surgeries completed by two years of age for optimal outcomes. Surgical treatment can achieve good alignment in the large majority of infants, independently of CP severity. However, success of surgical treatment to achieve repair of sensorial binocular fusion is dependent on severity of CP with improved outcomes for those with milder CP. Visual training programs for gains of attention to visual stimuli are very weakly recommended, although no adverse events are reported.

Limitations—While the search for the current review was comprehensive, and included review of grey literature, additional vision assessments and interventions may be available for infants at high risk for or with CP, as some reports did not meet our strict inclusion

criteria. Protocol-driven practice and expert opinion publications may add to the current body of knowledge and reduce the gap in available research literature about effective assessments and interventions for infants and toddlers at high risk for CP. The large majority of identified assessment tools were currently in clinical practice and thus could be considered reference assessments. Additionally, many of the studies included in this review were published before tools and guidelines for early detection of CP were developed, limiting the specificity of assessments and interventions in this age range.

Conclusion—The assessments and interventions for infants at high risk or with CP are sparse. However, clinical ophthalmological methodologies can effectively characterize the structural, neurophysiological and functional characteristics of CVI in this population. No recommendations can be made at this time for CVI-specific behavioural assessments of visual function in this population of infants. Few promising interventions for CVI have been identified, and they are not specific to infants with CP.

The results of this review underline the gap in targeted and rigorously validated assessments to allow early recognition and characterization of visual impairments in infants at high risk and with CP, to differentiate them from other non CVI problems. This type of future research may allow the design and evaluation of novel of interventions. In particular, measurement of preventive treatment efficacy could leverage existing quantitative visual tools. Early interventions could differentiate treatments for infants with CP with CVI from those without, and build on parent-infant transaction models proven effective in early rehabilitation of other CP-related impairments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Assessments

Figure 2.
Interventions

Table 1

COSMIN Psychometric studies quality assessment

Study	Assessment	Reliability				Validity				Criterion validity	Responsiveness
		Internal consistency	Reliability	Measurement Error	Content validity	Structural validity	Hypothesis testing	Cross-cultural validity			
Newcomb et al, 2010(12)	CVI Range	poor	poor	x	x	x	x	x	x	n/a	

CVI = cerebral/cortical visual impairment
n/a not applicable to assess responsiveness to treatment

Table 2

Assessments

Item	Population	Qualifier for inclusion into this review	Age	Assessment (function) E: Electrophysiology N: Neuroimaging B: Behavioral	Conclusion	Type P: prospective R: retrospective
Baeteman et al, 2008(13)	Primary exotropia (n=47)	WM and GM injury hydrocephalus (n=47)	0-57	N: MRI (brain abnormality) B: OM (degree of deviation)	Higher chance of abnormal MRI if more than 10 degrees of deviation (p < 0.05)	P
Bassi et al, 2008(14)	Preterm <33w GA (n=37)	Preterm birth (n=37)	40-42 w	N: MRI, DTI (FA optic radiations) B: Neonatal Visual Assessment (Ricci 2008)	Optic radiations FA correlates with neonatal visual assessment score (p < 0.05)	
Biagioni et al, 2002(15)	Term infants, NE or stroke (n=19)	CP diagnosis (n=10)	10-13m	E: EEG (reactivity to eye closure, other abnormal features) N: MRI (optic radiations and occipital cortex involvement) B: Teller AC (visual acuity), KP (visual fields)	Higher chance of abnormal vision if EEG nonreactive to eye closure	R
Birch et al, 1991(16)	Primary CVI (n=132)	CP diagnosis (n=34)	0-134m	B: FPL, projected screens (visual acuity); pen light or toy (fixation and tracking)	Acuity deficit correlated with sensory motor skills (p<0.001), but not gross motor skills	R
Brodsky et al, 2002(17)	Cortical (n=50) and subcortical (n=50) visual loss	Preterm birth, hypoxic-ischemic injury, infectious encephalitis, meningitis, hydrocephalus, stroke (n<50)	Pediatric	N: MRI or CT (degree of injury and cortical/subcortical involvement) B: Teller AC (visual acuity); light, moving object, OKN (visual responses), OM (gaze deviation, strabismus, eye movements)	In cortical visual loss, horizontal conjugate gaze deviation, exotropia, and a normal optic disc appearance were significantly more common. In subcortical visual loss, tonic downgaze, esotropia, and optic nerve hypoplasia were significantly more common.	R
Cavascan et al, 2014(18)	Primary CVI (n=115)	Preterm birth, perinatal hypoxia, acquired hypoxia, hydrocephalus, trauma, infections (n=75)	2m-15y	E: sVEP (grating acuity deficit and inter-ocular acuity difference)	Grating acuity deficit was smaller if tested in first year (p<0.001) but larger with anti-epileptics (p<0.001). Inter-ocular acuity difference was larger with strabismus and nystagmus than orthoposition (p<0.02).	R
Cioni et al, 1996(5)	NE or cerebral hemorrhage (n=80)	NE, PVL, IVH, CP (n=80)	6-86m	N: optic radiations and visual cortex involvement (MRI) B: Teller AC (visual acuity)	Visual acuity deficit correlated to the severity of optic radiation (p<0.0001) and visual cortex (p<0.0001) involvement. Optic radiation involvement predicted visual outcome (accuracy 85.3%, sensitivity 84.5%, specificity 86.6)	P

Item	Population	Qualifier for inclusion into this review	Age	Assessment (function) E: Electrophysiology N: Neuroimaging B: Behavioral	Conclusion	Type P: prospective R: retrospective
Clarke et al, 1997 (19)	Primary CVI (n=44)	Structural brain lesion, meningitis, IVH, neonatal encephalopathy, preterm birth (n=25)	5-20m	E: flash VEP B: Keeler AC (visual acuity), fixation, light response (visual responses)	Association of early flash VEP (normal and abnormal) and vision outcome (p=0.05)	P
Cohen-Maitre et al, 2005 (20)	CVI + CP (n=11)	CP diagnosis (n=11)	18-72m	B: total fixation duration at a PL dual monitor presentation (visual attention to color/gray and movement/static)	Children with CVI exhibit visual preferences for color and for moving objects. No significant preference between colors.	P
Dutton et al, 1996 (21)	Primary CVI or other poor vision (n=120)	Brain disorders, PVL, hypoxic ischemia, IVH, hydrocephalus, stroke (n=90)	1-16 y	B: Snellen AC (visual acuity), Cardiff/Keeler AC (preferential looking) E: VEP (preferential looking) <i>And individualized vision assessments appropriate for each child</i>	Children without CVI may have cognitive visual dysfunction (15%). This includes problems with recognition, orientation, depth perception, perception of movement, simultaneous perception.	R
Eken et al, 1994 (22)	Preterm and term-born infants with and without brain damage (n=65)	Preterm birth, PVL, IVH, NE (n=33)	0-18m	B: Teller AC (ophthalmologic assessment, responses to blink, fixing, following) N: cranial ultrasound (brain damage qualification)	100% of children with PVL III, IV had 5 th centile VA	R
Eken et al, 1995 (23)	Preterm and term-born infants with and without brain damage (n=65)	CP outcome (n=11)	3-18m	B: Teller AC (acuity), Griffiths (developmental skills), OM (tracking, blink reflex, fixing and following) N: MRI or CT (optic radiations and visual cortex involvement)	Risk of developing CP is 46 times higher in infants with an acuity 10 th centile compared to those with normal acuity (95% confidence interval 5.4)	R
Fazzi et al, 2012 (24)	Primary CP and CVI (n=129)	CP diagnosis (n=129)	3m-15y	N: MRI (brain abnormality) B: Teller AC (binocular VA up to 2 years), OKN (monocular responses), kinetic perimetry (visual fields), OM (fixation, smooth pursuit, saccadic movements, ocular movements and motility) <i>Additional assessments with children over 2 years</i>	An interaction between CP type and primary visual dysfunction. Children with diplegia primary strabismus (90%), hemiplegia - refractive errors (88%) and altered visual field (64%), and tetraplegia - ocular abnormalities (98%), oculomotor dysfunction (100%), and reduced visual acuity (98%).	P
Frank et al, 1992 (25)	No spontaneous visual behavior (n=60)	Asphyxia, structural brain abnormalities, hydrocephalus, meningitis, encephalitis	6w-10 y	E: sVEP flash and pattern (acuity and contrast threshold)	Children with cerebral blindness have preservation of occipital VEPs to flash (more than pattern). Their later (as opposed to early) occipital VEP and pre-occipital responses are deviated or absent.	
Good et al, 2012 (26)	Primary CVI (n=34), controls (n=16)	Preterm birth, NE, hypoxia, infection (n=34)	5m-5y	E: sVEP (spatial contrast threshold and acuity grating)	In children with CVI contrast sensitivity improved with age (p<0.01), but grating acuity did not.	P

Item	Population	Qualifier for inclusion into this review	Age	Assessment (function) E: Electrophysiology N: Neuroimaging B: Behavioral	Conclusion	Type P: prospective R: retrospective
					Contrast and grating acuity thresholds did not correlate.	
Guzzetta et al, 2001(27)	Congenital or early acquired hemiplegic CP (n=47)	CP diagnosis (n=47)	8-52m	B: Teller AC (grating acuity), OKN (binocular horizontal visual responses), kinetic perimetry (visual fields), Griffiths DQ and WISC (developmental skills), OM (fixation and following) N: MRI (optic radiations, visual cortex, basal ganglia lesions)	Visual defects were not correlated with brain damage location and timing of MRI. OKN was abnormal in >50%. More than 80% were abnormal on at least one test.	R
Jan et al, 1990(28)	Ocular and cortical visual impairment (n=167) CVI in 69 of 167	Preterm birth, hydrocephalus, CP diagnosis (n=50)	4m-11y	B: 4-point light gazing scale (acuity)	In children with CP 31 were light gazers, 19 non-light gazers. Children with unilateral only lesions were never light-gazers (0 of 50). All light gazers had bilateral disturbance of the cortex.	P
Madan et al, 2012(29)	Very low birth weight infants with and without IVH I, II (n=65)	IVH I or II (n=13)	5-7m	E: sVEP (grating acuity, contrast sensitivity and Vernier acuity)	Children with IVH I or II have poorer grating acuity, contrast sensitivity and Vernier acuity than their VLBW peers (p <0.001)	P
McCulloch, 2007(30)	Children with mild to profound intellectual and/or motor impairments (n=76)	CP diagnosis n=12 of 18 under 2 years	7m-16y	B: Visual skills inventory: 16 item parent questionnaire (Visual skills), Keeler and Cardiff AC (vision acuity) E: VEP (level of impairment, acuity)	Inventory questions about visual recognition and visually mediated social interactions had some significant, but variable, correlations with VEP and acuity card results.	P
Mercuri et al, 1997(31)	NE or abnormal neurological signs (n=37)	NE, multifocal lesions (n=37)	5-31m	B: ABCDEFV (ocular movements, pupil response, refractive errors, binocular OKN), AC (acuity), kinetic perimetry with small white ball (visual fields, fixation shift), Griffiths DQ (development) E: s-s VEP (phase and orientation) N: MRI (lesions involvement)	Infants with diffuse involvement of occipital cortex and basal ganglia have the most severe abnormalities of visual function.	P
Mercuri et al, 1999(32)	NE or stroke (n=29)	NE, hemorrhagic ischemic lesions (n=29)	24 m outcomes	B: ABCDEFV (ocular movements, pupil response, refractive errors, binocular OKN), AC (acuity), vision behavior (visual fields, attention over distance, fixation shift), Griffiths DQ (development) E: s-s VEP (phase and orientation) N: MRI (lesions involvement)	Fixation shift, visual field assessment have 100% negative predictive value for abnormal DQ, while OKN has 100% positive predictive value for abnormal DQ.	P
Ricci et al, 2006 (33)	Primary PVL, preterm birth (n=12)	CP diagnosis (n=10)	12-24m	B: OKN (ocular movements), Teller AC (acuity), kinetic perimetry with	Children with more severe PVL had most severe impairment of	R

Item	Population	Qualifier for inclusion into this review	Age	Assessment (function) E: Electrophysiology N: Neuroimaging B: Behavioral	Conclusion	Type P: prospective R: retrospective
Ricci et al, 2011(34)	Primary preterm birth (n=145)	CP outcome (n=23)	Term, 3-12m	small white ball (visual fields, fixation shift) N: MRI (optic radiations, visual cortex, basal ganglia and thalami involvement) B: Moving object (visual tracking), Teller AC (acuity), kinetic perimetry with small white ball (visual fields, fixation shift), Griffiths Mental Development Scales (development) N: cranial ultrasound (brain abnormality)	vision function, also associated with atrophy of thalami.	P
Salati et al, 2001(35)	Primary NE (n=11)	CP diagnosis (n=11)	1-9y	B: Low vision checklist: (light perception, visual exploration, fixation, following, grabbing, grabbing a moving object, deambulation, OKN); Keeler AC (preferential looking)	Residual visual function in children with CVI was detected in 100% of patients. with checklist quotient score and AC.	P
Schenk et al, 1992(36)	Primary CP (n=164)	CP diagnosis (n=164)	6m-19y	B: Teller AC (cards)	More children with CP showed lower acuity using AC. Using both methods prevalence of CVI was 84%.	R
Uggetti et al, 1996(37)	PVL and CP (n=27)	CP diagnosis (n=27)	16m-8y	B: Teller AC (acuity) N: MRI (visual cortex, optic radiations involvement)	CVI in 63% of cohort. The degree of CVI correlated with PVL and occipital atrophy (p <0.0001)	P
Watson et al, 2007(38)	Primary CVI (n=39)	NE, hydrocephalus, PVL, childhood hypoxia, IVH, static encephalopathy, trauma, infection (n= 37)	1-16 y	E: sVEP (acuity and contrast sensitivity)	Half of the cohort had improvements after mean 6.5 years between assessments. Children with more severity had more improvements in visual acuity and contrast threshold.	R
Watson et al, 2010(38)	Primary CVI (n=33)	birth asphyxia, hypoxia, infection, PVL, trauma, static encephalopathy, hydrocephalus (n=25)	1-19 y	B: Berkeley Grating AC (forced choice preferential looking acuity) E: sVEP (acuity)	Degree of CVI in children was more accurately assessed with VEP initially. Behavioral reassessment ~ 7 years later and initial VEP not statistically different p=0.45	R
Yu et al, 2011(39)	PVL (n=24), controls (n=12)	CP diagnosis (n=24)	6-18m	N: fMRI (time to peak of hemodynamic response functions) B: Teller AC (binocular acuity)	Infants with PVL have deviated, weak, or absent PVC activation. Number of activated voxels in occipital lobe was correlated with the TAC assessment (p < 0.001)	P

AC = Acuity Cards

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CP = Cerebral Palsy
CUS = Cranial ultrasound
CVI = cerebral/cortical visual impairment
DQ = developmental quotient
fMRI=functional Magnetic resonance imaging
GAC = grating acuity cards
GAD = grating acuity deficit
IAD = inter-ocular acuity difference
IVH = intraventricular hemorrhage
KP = kinetic perimetry
MRI = Magnetic resonance imaging
NE = neonatal encephalopathy
OKN = optokinetic nystagmus
OM= oculomotor function
PHH = post hemorrhage hydrocephalus
PVC = primary visual cortex
PVD = posthaemorrhagic ventricular dilatation
PVL = periventricular leukomalacia
sVEP = sweep Visual Evoked Potential
s-sVEP = steady state Visual Evoked Potential
VA =Visual acuity
VEP = Visual Evoked Potential
VLBW = Very Low Birth Weight

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Table 3

Interventions

Item	N	Intervention	ES Cohen's <i>d</i>	Design	Comments	Grade
Ghasia et al, 2011(40)	50, all CP	Operative (esotropia and exotropia surgery)	NR	observational, cross-sectional, prospective study		Low
Jacobs et al, 2013(41)	328; 252 with CP	therapeutic hypothermia	typical RR 0.57 (95% CI 0.30, 1.08), typical RD -0.06 (95% CI -0.13, 0.01)]	Systematic review	encephalopathic asphyxiated newborn infants 8 trials	High
Lanners et al, 1999(42)	76; 15 with CP	multiple: including black and white, and colored slides, black light and fluorescent material, snoezelen multisensory experience	n/a	Clinical review, group case studies	visual and intellectual disabilities	Very Low
Natalucci et al, 2016 (43)	448; 16 with CP	reypo or placebo	0.3	RCT	26-31 birth GA	High
Schmidt et al, 2012(44)	1640; 182 with CP	caffeine therapy	0.18	RCT follow-up	Mental Development Index score 1 SD below the mean	High
Schulzke et al, 2007(45)	552	therapeutic hypothermia	NR	Systematic review	5 trials	High

CP = cerebral palsy

NR = not reported

RCT = randomized controlled trial

GA = gestation age

SD = standard deviation

Table 4

AMSTAR methodological quality rating checklist

Items											
1	2	3	4	5	6	7	8	9	10	11	
Schulzke et al,(45)											
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Jacobs et al, (41)											
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y = Yes; N= No;?=Can't Answer; N/A=Not Applicable

The AMSTAR methodological quality rating items are: (1) Was an “a priori” design provided? (e.g. inclusion/exclusion criteria) (2) Was there duplicate study selection and data extraction? (e.g. 2 independent assessors); (3) Was a comprehensive literature search performed? (4) Was the status of publication (i.e., grey literature) used as an inclusion criterion? (5) Was a list of studies (included and excluded) provided? (6) Were the characteristics of the included studies assessed and documented? (7) Was the scientific quality of the included studies used appropriately in formulating conclusions? (8) Was the scientific quality of the included studies assessed and documented? (9) Were the methods used to combine the findings of studies appropriate? (10) Was the likelihood of publication bias assessed? (11) Was the conflict of interest included?

Table 5

Cochrane Risk of Bias Table for Randomized controlled trials

Reference	Random	Sequence generation	Allocation	Concealment	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete Outcome data addressed	Free of selective reporting	Free of Other bias
Schmidt et al, (43)	H		H		U	L	H	H	H
Natalucci et al, (42)	H		H		H	L	H	H	H

L= Low ; U= Unclear; H= high