Disorders of vision in neonatal hypoxic-ischaemic encephalopathy – A systematic review

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Abstract

Objective

Neonatal Hypoxic-Ischaemic Encephalopathy (HIE) following perinatal asphyxia in term infants is associated with neonatal mortality and a high risk of neurodevelopmental impairment later in life. Visual disorders are an accepted complication of HIE and the association has been cited in the literature many times. This review aims to study the evidence for this association and assess the quality of the data on which this is based.

Design

A systematic literature review was conducted and 922 citations were assessed using standard methods outlined by the PRISMA protocol.

Results

The results demonstrate that the majority of studies have reported on various neurodevelopmental outcomes but rarely vision. Based on limited currently available data, extracted from a number of small studies, an association of neonatal HIE with visual impairments seems to exist but detail is lacking. Notably, in the existing studies there is a striking lack of consistency in the methods used to diagnose HIE and, similarly, a wide variation in the methods employed to measure visual function.

Conclusions

To explore the observed association further in terms of prognosis and the effects of HIE treatments on visual outcomes, future studies will need to address the issues of standardised diagnostic criteria, severity grading and robust, age-appropriate visual assessment.

Introduction

Hypoxic-ischaemic encephalopathy (HIE), a consequence of perinatal asphyxia in term born infants, has an estimated incidence of 1.5 per 1000 live births in high-income countries and is associated with a high risk of mortality and neurodevelopmental impairment[1-3]. Cerebral Palsy (CP) and global developmental impairment are the most investigated outcomes, while impairment of vision is less explored[4-6]. Hypoxic-ischaemic brain damage is often seen in the basal ganglia, thalami, cortex, optic radiation, and cerebellum; brain areas which are crucial for normal visual development[7,8]. Cerebral Visual Impairment (CVI) is a likely outcome of these insults[9]. Sakki et al conducted a systematic review of definitions and terminology of childhood CVI and proposed the following definition: childhood cerebral visual impairment is a verifiable visual dysfunction which cannot be attributed to disorders of the anterior

visual pathways or any potentially co-occurring ocular impairment[10]. Visual field loss, complete vision loss, difficulty interpreting visual inputs, carrying out functions related to vision, as well as strabismus, and reduced acuity are observed clinically in neonatal HIE[11-15]. There is a generally clinically accepted association between neonatal HIE and visual problems. However, evidence for incidence and severity of visual impairment, details of the types of visual disorders, and specific associations with severity of hypoxic-ischaemic brain injury apper to be unclear.

This systematic review aims to evaluate current evidence and identify which questions are yet to be answered with regards to visual disorders in neonatal HIE. By understanding more about specific visual outcomes professionals may be able to develop new prognostic tools, evaluate treatments specifically with regard to visual outcome, and develop novel diagnostic criteria.

Methods

Search Strategy

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods[16], as well as taking guidance from the Centre for Reviews and Dissemination[17]. A review protocol was specified in advance and registered on the international prospective register of systematic reviews: PROSPERO (registration number: CRD42017076511). Inclusion and exclusion criteria for the studies assessed were:

- Randomised controlled trials (RCTs) and observational studies were eligible for inclusion in the review.
- Studies assessing term born (>36+6 weeks of gestation) infants with HIE were

included. Studies including preterm infants but with distinguishable data for term versus preterm infants were also included.

- Studies were only included if the exposure of HIE was clearly stated. Patients diagnosed as mild, moderate, or severe HIE were included. Neonatal encephalopathy (NE) was accepted but only if the aetiology of perinatal asphyxia was made clear. Studies reporting data on other aetiologies were included only if there was distinguishable separate data for HIE versus non-HIE status.
- Any appropriate visual impairment assessed was an eligible outcome criterion for the review. Questionnaire surveys were excluded as eligible data for assessment of vision. Studies in which a specific vision test or assessment had been performed were used in our primary analysis. A secondary analysis was carried out which also included studies with no direct testing, but a statement about being registered as "Sight Impaired" or "Severely Sight Impaired" (previous "Partially Sighted" and "Blind" respectively), or having cortical visual impairment without description of how this was diagnosed.
- Excluded were animal studies, studies only including preterm (<37 weeks of gestation) infants, and studies with causes of NE other than perinatal asphyxia. Studies not in the English language, published before 1997, or not available on any of the databases mentioned below were excluded.

Published articles, abstracts, and conference proceedings reporting visual outcome in term-born infants with HIE published between 1997-2019 (last literature search performed on January 1, 2019) in the English language, available on at least one of the databases MEDLINE, EMBASE, Web of Science, or The Cochrane Central Register of Controlled Trials

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were included. Grey literature was searched by using the Open Grey database. The following search terms were used: *Infants, New-borns, Neonates, Perinatal asphyxia, Neonatal encephalopathy, Hypoxic-Ischaemic Encephalopathy, Cortical visual impairment, Cerebral visual impairment, Cognitive impairment, Sensory impairment, Visual function, Visual impairment, Visual-motor impairment, Visual perception.* Appendix 1 shows an example of a search strategy used for MEDLINE(Ovid) electronic database. Screenning was done by two independent reviewers; discrepancies were resolved by discussion and a third reviewer (EN, JES or BV). The stages of screening were (1) title screening, (2) abstract screening, and (3) full-text screening. A screening and selection tool describing inclusion and exclusion criteria was developed and pilot tested on two randomly selected studies, then modified and used by all reviewers on every citation. Full text papers were obtained for the citations that were deemed to be appropriate to include by both reviewers. The full-text papers were screened to eliminate any studies not meeting the inclusion criteria.

Quality Assessment

Quality of the selected studies was assessed using the Cochrane Risk of Bias Tool and a modified version of the Critical Appraisal Skills Programme (CASP) checklists. The Cochrane Tool was used for all RCT trials, as it is considered the gold standard for appraisal of RCTs, and the CASP checklists were used for quality assessment of observational studies. Bias was analysed by assessing the categories of random sequence generation, allocation concealment, blinding of personnel, participants, and outcome assessment, attrition bias, reporting bias, and other bias (such as funding and author affiliations). Quality assessment was done before data extraction. Studies of low quality were not excluded, but their impact on the results of the review are summarised in the discussion.

Results

The search initially identified 1069 citations (32 from the Cochrane Library, 210 from MEDLINE, 507 from EMBASE, 320 from Web of Science), resulting in 922 citations after duplicate removal. The titles of the 922 citations were screened, leaving 178 citations available for screening of the abstracts. After abstract screening, 35 citations were identified and full-texts were obtained. Citations that were not included after full-text screening and their reason for exclusion are listed in Appendix 2. After completion of all stages of screening and selection, six studies were included for narrative synthesis in the primary analysis and 5 studies in the more inclusive secondary analysis. No unpublished relevant studies were identified in the search for grey literature. See Figure 1 for a summary of the screening process.

Of the six studies included, all (100%) reported evidence of some form of visual impairment (See Table 1), including but not limited to reduced visual acuity, nystagmus, cortical visual impairment, and refractive errors . This is as expected as the visual processing areas of the brain, such as the cortex, striatum, optic radiation, and cerebellum are affected by HIE, there is likely to be an increased risk of visual dysfunction.

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Author, Year	N	N_{HIE}	Age	Sex (% Male)	Quality of Method of diagnosis of HIE	GA	Primary Outcome(s) Measured
Azzopardi, 2014	325	184	Outcomes measured at 6 to 7 years.	50% in hypothermia group, 63% in control group		>36 weeks	Frequency of survival with an IQ score of 85 or higher.
Casteels, 1997	19	5	Ages ranged from 6 to 8 weeks at presentation.	58%		5 infants ≥36 weeks gestation	Correlation between MRI findings and development of CVI
Lim, 2005	19	19	Median age at first visual acuity was 15 months (range, 6-36).	-		≥36 weeks gestation	Visual acuity development.
Mercuri, 1999	29	18	2 years	-		≥36 weeks gestation	Result of visual test at 5 months and correlation with neurodevelopment at 2 years.
Salati, 2002	56	19	Mean age was 7 years 1 month, SD 4 years.	66%		Mean 34 weeks (range 26-41)	Features of ocular motility.

Table 1: Data Extraction Form – Participant Characteristics and Study Results

N = total number of participants included in the study
N_{HIE} = total number of term-born HIE participants fitting the inclusion criteria of this review included in the study
Quality of method of diagnosis of HIE:
= Good quality diagnoses of HIE based on a combination of clinical factors
= Diagnosis of HIE based only on neuroimaging
= Method of diagnosis of HIE is unclear or not stated
GA = gestational age

The six studies yielded a total number (N) of 618 participants. However, not all of the participants fit the inclusion criteria. A modified participant number (N_{HIE}) was created to identify the number of participants in each study who were term born infants diagnosed with HIE. In total, 283 participants (N_{HIE} = 283) fit the inclusion criteria, and evidence of visual impairment was analysed by creating a fraction (X/N_{HIE}), where X = number of term born HIE infants with evidence of visual impairment, over the total number of term born HIE infants included in the study. Overall, 35.33% of infants displayed some form of visual impairment according to the measures included in that study. However, the methods of visual assessment were extremely broad ranging from detailed electrophysiological assessments to simple parent reported questionnaires including basic questions such as 'is

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your child blind' (see Table 2 for details).

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Author, Year	Available Visual Outcome Data	Summary of results of Visual assessment	X / N_{HIE} (%)
Azzopardi, 2014	Visual impairment not corrected by glasses or blindness reported by questionnaire.	Evidence of high rates of visual impairment in term-born HIE infants.	19/184 (10.33%)
Casteels, 1997	Blindness, object and light perception and visual acuity measured subjectively with bright light targets or Ffooks test in older children.	Evidence of high rates of visual impairment in term-born HIE infants.	2/5 (40.00%)
Huo, 1999	Diagnosis of CVI. Defined as: Vision loss in absence of signs of anterior visual pathway disease or vision loss greatly exceeding that which would be expected given the findings of an ocular examination. Information retrieved from medical records.	Evidence of high rates of visual impairment in term-born HIE infants.	38/38 (100.00%)
Lim, 2005	Visual acuity Nystagmus, strabismus, and optic atrophy. Visual acuity was measured by "Longitudinal measures of grating acuity were obtained using preferential looking (PL) and visual evoked potential (VEP) procedures"	Evidence of high rates of visual impairment in term-born HIE infants.	18/19 (94.74%)
Mercuri, 1999	Summary of number of abnormal visual assessments including: ocular movements, pupil response, refractive errors, binocular optoki- netic nystagmus (OKN), Acuity by preferential looking, visual fields (using Stycar ball, fixation shift and Visual evoked Potentials	Evidence of high rates of visual impairment in term-born HIE infants.	11/18 (61.11%)
Salati, 2002	Visual assessment included viual acuity and an accurate examination of ocular motility, anterior segment, refraction in cycloplegia, and fundus oculi. Fundus was explored with indirect ophthalmoscopy after dilation of the pupil. Accommodation was not assessed. Flash visual evoked potentials also assessed.	Evidence of high rates of visual impairment in term-born HIE infants.	12/19 (63.16%)

Table 2: Summary of Visual Assessment Outcomes

X = total number of term-born infants with HIE fitting the inclusion criteria for this review included in this study who have some form of visual impairment

Infants with a known diagnosis of CVI who were retrospectively studied to check for HIE as the primary cause were included, and data distinguishable for them can be found in Table 3.

Author, Year	N	N_{HIE}	Age	Sex (% Male)	Quality of Method of diagnosis of HIE	GA	Primary Outcome(s) Measured
Huo, 1999*	170	38	Average patient age was 3 years.	-		-	Frequency of various aetiologies of CVI.

Table 3: Studies assessing infants with a known diagnosis of CVI who were studied retrospectively

There were 5 studies who were otherwise eligible, but used registration as SI/SSI (PS/BL), or CVI with undefined diagnostic criteria as their outcome. These studies are listed in Table 4 and together included 1086 infants. The proportion of children who were certified with sight loss was 55 and if included with children in our primary analysis, overall 155 children were repored as having impaired vision.

Author, Year	N (cooled)	N (control)	Age	GA	Primary Visual Outcome(s) Measured	X / N_{HIE} (%) Hypothermia group	X / N_{HIE} (%) Control group
NICHD Study	102	106	Outcomes measured at 18 to 22 months of age	≥36 weeks	Blindness	7.0%	14.0%
CoolCap Trial	116	118	Outcomes measured at 18 months of age	≥36 weeks	Cortical visual impairment – diagnosis not defined	10.0%	17.0%
TOBY Study	163	162	Outcomes measured at 18 months of age	≥36 weeks	No useful vision	7.0%	11.0%
ICE Study	107	101	Outcomes measured at 2 years of age	39 weeks (SD 1.8)	Legal blindness	1.3%	0.0%
Neo.nEURO	53	58	Outcomes measured at 18-21 months of age	≥36 weeks	Cortical visual impairment – diagnosis not defined	3.1%	5.0%

Table 4: Studies Eligible but with reports of "Blindness" or CVI without diagnostic criteria as visual outcome measures

Discussion

This review offers evidence of visual impairment in HIE and, importantly, identifies huge variability in the techniques of visual assessment used. The citations included in this review show an overall trend of high rates of visual impairment. However, the variety of definitions and diagnostic criteria for HIE and the abundance of different and often outdated visual assessment tools contributes to the significant heterogeneity amongst the studies. This is likely to be because of the well recognised difficulties in testing very young children, especially those with disabilities, and the wide range of available tests.

The participants' age in each study was variable. As children develop, their visual system is constantly changing and therefore assessments of vision at different ages cannot be deemed comparable. According to *Tresidder et al,* "delayed visual maturation" may also affect visual function assessments in this group[18]. In the first months of life, the extrageniculate system is predominant in infants while later, the geniculostriate visual system develops[18]. The latter is associated with development of the ptic tracts, optic radiations, and occipital cortex, key pathway components of the visual system[18].

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It is important to note that studies did not correlate visual outcome with co-morbidities such as CP, global cognitive impairment, or epilepsy despite these conditions significantly affecting the ability of children to perform visual tests.

There is little specific research and evidence on this particular topic[19-22]. Studies tend to assess "blindness" as the only available visual outcome data[11,13-15] . The use of registered sight impairment has the advantage of being available from parent, clinician or routine data sources and is relatively easy to explain and collect. The disavatage is that children who are not registered may still have functionally important visual impairments and so the overall visual mobidity may be undersestimated unless direct assessments of vision are carried out. Specific visual impairment measurements are either lacking, inconclusive, or conducted with inappropriate visual assessment tools[23-25]. This is in contrast to the wealth of information available on visual impairment in the preterm population which, due to the rapid changes in brain development before term, cannot be applied to term HIE. The lack of published data on long-term visual outcomes of term neonatal HIE leaves a gap in evidence resulting in a lack of information for patients and their families, a lack of knowledge regarding the efficacy of interventions and results in inconsistencies in clinical management and screening[4-6]

Issues Relating to Population

Only *Lim et al*[26] looked exclusively at visual function in term born infants with HIE. All other studies (83% of the included studies) had different primary outcomes and not all of the participants met our inclusion criteria. Two studies (33%)[23,27] included preterm infants, and two studies (33%)[9,28] included non-HIE patients. However, as there was statistically distinct and exclusive data in all of the studies for termborn HIE patients, these studies were included and data was extracted from participants fitting the inclusion criteria. During data

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extraction, N_{HIE} was created as a modified population measure, to reference the number of participants included in each study who fit the inclusion criteria specifically. Contamination of the studies with preterm infants and new-borns without HIE would have altered the results. This modification of the study population cut down the total population by a significant amount, median 25.5 (range 0 - 141) for each study, and from 618 to 283 in total. *Huo et al*[9] looked at case records of 7200 patients to identify infants diagnosed with CVI. Of the 170 resulting cases, 38 had the aetiology of HIE. *Mercuri et al*[29] had a population of 29, but included infants who were not diagnosed with HIE. As this study also showed separate individual data for each participant, N_{HIE} could be calculated without contaminating the data with non-HIE patients. There is an evident lack of studies looking at term born HIE infants exclusively, and as outcomes can differ between term born versus preterm newborns, high quality studies are required to be able to access data exclusive to this group of patients.

Issues Relating to HIE Diagnosis

Of the six studies included, only two (33%) diagnosed HIE based on a combination of clinical factors. Three studies (50%) did not describe how HIE was diagnosed, and one study (17%) based the diagnosis of HIE on neuroimaging only. The highest quality HIE diagnosis was done by *Azzopardi et al*[14], who used a combination of examining the infant for altered signs of consciousness, measuring APGAR scores, as well as evaluating biological markers such as acidosis, and base deficit in umbilical cord or blood sample. No study mentioned evidence of multi-system organ failure consistent with hypoxic-ischemic damage. Previous research has shown that the most variable data and unpredictable outcome is for those infants who are diagnosed with "moderate encephalopathy"[5]. Since no studies reported statistically exclusive data for participants with different severities of encephalopathy, no further

information can be extracted about visual outcomes in relation to HIE severity. This indicates a significant gap in knowledge which prevents the development of evidence based, standardised screening, counselling or treatment pathways.

Issues Relating to Appropriate and Universal Vision Assessment

The six studies included measured different aspects of vision, and used assessment tools that were unique to their specific outcome and study aim and therefore are not directly comparable. Studies where only CVI patients were included[9,27] and the aetiology was retrospectively studied will have contaminated the results as it can be assumed that all participants will have visual impairment due to CVI. Therefore, these were reported separately in Table 3. Perceived wisdom on visual outcomes for term HIE has been brought about by extrapolation from such studies, as no real rate of CVI among HIE infants could be identified, and no statistical comparison between the visual outcomes for HIE versus healthy newborns has been made. Measures of visual outcome as part of cognitive and behavioural assessment tools as well as measures done via surveys and questionnaires were not considered appropriate tools of visual assessment since they are not developed specifically for visual assessment and results obtained from these assessments may be affected by non-visual components. *Mercuri et al*[28] assessed visual function based on acuity, visual fields testing, fixation shift, and VEP's. However, in reporting the visual assessment, only "number of abnormal visual tests" was recorded for every individual. Even though a summary of other visual assessments was discussed, they were not correlated with each individual participant and therefore data could not be extracted for term HIE (N_{HIE}) infants specifically. *Casteels et al*[23] used the fFooks test to measure visual acuity. This study was included as we searched for *any* evidence of visual impairment. However, it should be noted that this test is

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no longer considered valid due to lack of crowding and proper resolution. In most cases, only VEP was used to measure "vision", and results of infants with HIE were not separated from those with different diagnoses or no separate statistical analysis was done for term versus preterm infants. Studies reporting only "blindness" as visual outcome data were not included in the primary analysis of this study, as it is a blunt category, and papers did not describe how exactly "blindness" was diagnosed. Many studies use only questionnaires or surveys sent out to parents of infants to assess for the presence of blindness. The secondary study which included these studies, however, had much larger sample sizes, and therefore a better representation of the instances of visual impairment in infants born with HIE.

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Many randomised-controlled trials assessing the effects of hypothermia treatment on neurodevelopmental outcomes of HIE only assessed for the presence of "blindness", making the effect of hypothermia treatment on visual outcomes difficult to interpret. However, these studies had by the best method of diagnosing and assessing HIE, and provided critical information to determine the effects of cooling/hypothermia treatments on neurodevelopmenta outcomes in infants born with HIE.

Overall, although these studies included visual data, none is comparable to other data due to wide variety of testing methods and variable age of testing in infants.

Study Strengths

Three individual reviewers discussed every decision thoroughly to minimise bias. Narrative summaries were extracted from original articles precisely, further minimising bias and reviewer intervention with study results.

Study Limitations

The most significant limitation was heterogeneity of the included studies. Substantial differences in study design, HIE diagnosis and visual assessments resulted in varying outcomes. Different outcome measures were used in each of the studies. Reporting of participant characteristics varied in each of the studies. Therefore, data was not deemed sufficient to perform a meta-analysis. Most of the studies had small sample sizes and therefore may lack power and not be considered representative. Language restrictions meant that no studies published in languages other than English could be included. These limitations pertain to the strength of the association between term HIE and visual dysfunction but highlight the key finding of this review, which is the striking lack of robust data on visual function in this group of infants.

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Conclusions

The evidence from this review supports the commonly held assumption of a correlation between neonatal HIE and visual impairment. However, variability in diagnosing, treating, and measuring the severity of HIE and lack of robust and validated visual function measures hinder studies aiming to report on visual impairment in this condition. Future prospective, long-term, masked studies using standardized methods for HIE diagnosis/severity and visual assessment for children the same age, would be necessary in order to shed light on this known, but currently under-evidenced association. This would facilitate future studies into preventative strategies for visual impairment caused by HIE and the impact of therapeutic hypothermia, and other potential interventions, on visual outcomes. Importantly, it would provide prognostic and screening information for clinicians and improve management.

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All persons listed as authors for this review meet the criteria for authorship and were involved in the design, analysis, and review of the paper and take full responsibility for the content of this review. Conception and design of the study was mainly carried out by Dr. Brigitte Vollmer and Mr Jay Self, and analysis of selected papers and research method was carried out by Ms. Eva Nagy, with Dr. Cathy Williams acting as a main reviewer as well.

There are no other persons who made significant contribution to this work.

What is already known on this topic

Neonatal hypoxic-ischaemic brain injury often affects brain areas which are crucial for normal visual development

There is a generally clinically accepted association between neonatal HIE and visual impairment

What this study adds

Evidence for visual impairment in neonatal HIE seems strong but details of what this comprises is lacking

Existing studies employ a large variety of different, often very subjective, ways of assessing visual outcomes of neonatal HIE

There is a need for development of protocols on standardised diagnostic criteria and standardised protocols for age-appropriate assessment of visual function in neonatal HIE

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