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Neonatal hypoglycaemia and visual development: A Review


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Abstract:

**Background:** Many newborn babies experience low blood glucose concentrations, a condition referred to as neonatal hypoglycaemia (NH). The effect of NH on visual development in infancy and childhood is of interest because the occipital lobes, which include the primary visual cortex and a number of extra-striate visual areas, may be particularly susceptible to NH induced injury. In addition, a number of case series have suggested that NH can affect eye and optic nerve development.

**Objective:** To review the existing literature concerning the effect of NH on the visual system. **Methods:** A PubMed, Embase, Medline and Google Scholar literature search was conducted using pre-specified MeSH terms. **Results:** The literature reviewed revealed no clear evidence for an effect of NH on the development of the eye and optic nerve. Furthermore, occipital and occipital-parietal lobe injuries following NH often occurred in conjunction with co-morbid conditions and were not clearly linked to subsequent visual dysfunction, possibly due to difficulties in measuring vision in young children and a lack of studies at older ages. A recent, large scale, prospective study of NH outcomes at 2 years of age found no effect of mild to moderate NH on visual development. **Conclusion:** The effect of NH on visual development is unclear. It is currently unknown whether NH affects visual function in mid to late childhood when many visual functions reach adult levels.

Key words: Neonatal hypoglycaemia, vision, occipital cortex, visual function
After birth, maternal glucose delivery across the placenta ceases and neonatal blood glucose concentrations fall, before rising again after the first few hours to reach adult concentrations around day 3. However, between 5-15% of newborn babies experience low blood glucose concentrations, a condition referred to as Neonatal Hypoglycaemia (NH)[1]. Risk factors for NH include maternal diabetes, preterm birth and being small or large for gestational age. NH may be accompanied by symptoms such as seizures, but is also commonly asymptomatic. Therefore, it is usual for at risk babies to undergo blood glucose monitoring and to be treated for NH if their blood glucose concentration falls below a specific threshold. A threshold of 2.6 mmol/l is widely used [2,3], and children treated at this threshold have recently been reported to have normal neurologic outcomes at 2 years of age [4]. Periods of severe NH are associated with brain lesions and impaired neurodevelopment [5] and mild episodes of NH may also be associated with abnormal neurodevelopment [6]. The impact of NH on vision is of interest as NH may preferentially damage the occipital-parietal region of the brain that is centrally involved in visual processing [7].

Here we review the literature relating NH to the development and function of the visual pathway. Blood glucose concentrations, patient age ranges and the presence or absence of symptoms are provided at the first mention of each study if this information was available.

We searched PubMed, Embase, Medline and Google Scholar using the following MeSH terms: neonatal hypoglycaemia and brain injury, neonatal hypoglycaemia and vision or visual development or ophthalmological findings, neonatal hypoglycaemia and cortical/cerebral visual impairment, and neonatal hypoglycaemia and neurodevelopment. The search was completed in June 2016. Primary research
articles written in English that reported data from patients of any age who had experienced hypoglycaemia during the neonatal period (< 1 month of age) were included in this review. No restriction was placed on the age of the published articles. We found that the literature on NH and vision is dated with only five contemporary studies (< 5 years old) identified. This was surprising given that NH and impaired vision are often linked in the general literature relating to NH.

Neonatal hypoglycaemia and ocular development

Two older case-series studies have linked NH to cataract [8,9]. For example, in a case series of 13 children with cataracts and documented episodes of low blood glucose concentrations at different ages, three children had experienced NH (0.6 to 1.1 mmol/L) [9]. Cataract formation following hypoglycaemia (< 2.0 mmol/L) in the adult rat has been linked to low aqueous humour glucose concentrations and reduced concentrations of adenosine triphosphate, a coenzyme that contributes to lens transparency [10]. However, it is unknown whether similar effects occur in humans. In fact, more recent studies have not identified an association between NH and cataract [11] and an older follow-up study of children between the age of 1 and 4 years who had experienced NH (< 1.66 mmol/L) reported cataract in only one of 151 cases [6]. Furthermore, any association between NH and cataract could also be secondary a common underlying risk factor such as low birth weight [12].

Optic nerve hypoplasia has also been associated with NH. A retrospective review of patients with optic nerve hypoplasia [13] found that 6 of 51 children (12%) had experienced NH (< 1.38 mmol/L for preterm and < 1.94 mmol/L for full term babies).
However, a larger prospective study of optic nerve hypoplasia revealed that only 5 of 93 (5%) children with optic nerve hypoplasia had experienced NH [14].

Optic nerve hypoplasia originates \textit{in utero} [15,16]. Therefore, any association between NH and optic nerve hypoplasia is likely to be indirect. Interestingly, a study of children born to diabetic mothers [17] reported a relatively high prevalence of optic nerve hypoplasia (17 of 93 patients) compared to the general population (7 to 10 per 100,000) [15,18]. This suggests that certain conditions may increase the risk of both NH and optic nerve hypoplasia, since 50% of babies born to diabetic mothers will develop NH [19].

Macular hypoplasia [20], bilateral optic atrophy [21] and congenital glaucoma [22] have also been reported in cases of NH. However, these children had experienced a range of comorbid conditions, making it unclear whether NH was directly related to the ocular pathologies.

In summary, a link between NH and ocular development has not yet been clearly demonstrated.

**Neonatal hypoglycaemia and refractive error**

The refractive status of children with a history of NH has been described in two studies. Koivisto \textit{et al.} assessed 151 children from 1 to 4 years of age who had experienced hypoglycaemia after birth (< 1.66mmol/L). Of these, one child who had experienced symptomatic hypoglycaemia with convulsions had high myopia associated with zonular cataract, and one who had experienced asymptomatic hypoglycaemia had high hyperopia [6]. Karimzadeh \textit{et al.} reported a higher proportion of refractive error, with 6 of 27 Iranian children (22%) who had
experienced NH (< 1.1 mmol/L) having refractive error (type unspecified) at a mean age of 3.5 years [23]. However, this prevalence of refractive errors is similar to that reported among school aged children in Iran (27%) [24]. Therefore there is no current evidence for a clear link between NH and refractive error.

**Neonatal hypoglycaemia and binocular vision**

Three studies have indicated a possible association between NH and strabismus. Koivisto et al. reported strabismus in 10 of 144 (7%) children aged 1 to 4 years with a history of NH (< 1.1 mmol/l; 7 symptomatic, 3 asymptomatic) [6]. However, this rate of strabismus was comparable to their non-hypoglycaemic control group (3 of 54, or 6%), suggesting that NH may not have been a contributing factor. Murakami et al. reported strabismus (type unspecified) in 1 of 8 children (13%) at a mean age of 4 years who had experienced symptomatic NH (<1.1 mmol/L) [25] and Yalnizoglu et al. found that alternating exotropia was present at a mean age of 3 years in 1 of 13 children (8%) with a history of symptomatic NH [21]. Small sample sizes make it difficult to draw strong conclusions from these studies. Furthermore, strabismus is common following neurological insults and therefore co-morbid conditions other than NH may have contributed to these associations. Nystagmus has also been reported in a small number of infants with a history of NH [6] but, as with strabismus, a direct link with NH has not been established.

**Neonatal hypoglycaemia and brain injury**

Severe or prolonged NH can result in ischemic and atrophic brain injury, affecting the cortex and underlying white matter [5]. Case and retrospective cohort studies involving brain imaging have suggested that the occipital and posterior parietal lobes
are particularly susceptible to brain injury associated with NH [7,20,26]. For example, NH (<2.2 mmol/L) was identified as the primary cause of brain injury in 13 of 21 infants with occipital lobe abnormalities [27].

Brain imaging data from case and cohort studies of NH are difficult to interpret due to the high prevalence of co-morbid conditions such as hypoxia-ischemia or intrauterine growth restriction, both of which are also associated with brain injury [5, 21, 28]. In addition, a mechanism that could explain an association between posterior brain injury and NH has not yet been identified. However, the possibility that NH preferentially affects posterior regions of the brain is of particular interest with regard to vision because visual brain areas are concentrated within the occipital lobe and extend anteriorly to the parietal and temporal lobes. Injury of the optic radiations following NH has also been reported with clear implications for visual processing [7].

The proposal that NH is associated with localized damage to posterior brain areas was not supported by a relatively large retrospective cohort study of infants with a history of NH (n = 35), although all had intrauterine growth restriction and 4 had additional endocrine disorders [5]. This study reported diffuse, widespread injuries evident on magnetic resonance imaging (MRI) obtained up to six weeks after birth. Nevertheless, 29% of the cases reported in this study had a posterior pattern of brain injury, compared to only 6% with an anterior pattern.

**Neonatal hypoglycaemia and cortical processing of visual information**

As might be expected from the finding that visual brain areas can be affected by NH, visual impairments characteristic of abnormal cortical processing have been reported
in babies and children who experienced severe or recurrent symptomatic NH (0.1 to
1.1 mmol/L) [25,29]. Tam et al. conducted a retrospective case review of 45 infants
who had experienced NH (<2.6 mmol/L) and had also undergone diffusion-weighted
brain imaging [20]. Diffusion restriction within the occipital lobe was evident in 8
(18%) infants indicating potential injury to visual brain areas. No occipital lobe
diffusion restriction was observed in babies who were imaged six days or more after
experiencing NH, suggesting that recovery from diffusion restriction may occur soon
after NH.

Despite the high rate of occipital lobe diffusion restriction reported by Tam et al., only
2 of the 18 infants (11%) for whom follow-up data were available were classified as
having cortical visual loss when assessed at 4 to 8 months’ corrected age. Both of
these infants experienced NH for 2 days or more and had occipital lobe diffusion
restriction on earlier scanning. One infant was diagnosed with cortical blindness
indicative of bilateral occipital lobe injury and the other with homonymous
hemianopia indicating a unilateral injury.

Visual evoked potentials (VEPs) were also measured in 20 of the infants studied by
Tam et al. at the corrected age of 4 to 8 months. Abnormal VEPs were reported in 11
infants (55%). Details of the VEP protocol were not provided; however, as was the
case for diffusion restriction, abnormal VEPs were not predictive of adverse visual
outcomes.

The absence of a direct relationship between patterns of occipital lobe brain injury
and visual deficits is also evident in a number of smaller case series and
retrospective case reviews involving infants with NH. For example, Murakami et al.
found that 7 of 8 infants and children who had experienced NH (< 1.1 mmol/L) exhibited parieto-occipital lobe injuries, although only 3 of these developed impaired visual acuity [25]. Similarly, Filan et al. reported only one infant with visual impairment of four cases with NH (< 1.5 mmol/L) and occipital brain injury [7]. Burns et al. found a reasonably consistent association between posterior brain injury and visual deficits (11 of 35) in their NH cohort (median blood glucose concentration 1.0 mmol/L) when assessed at a minimum age of 18 months, although formal vision testing was not conducted, so vision problems may have been under- or over-estimated [5]. They mention that although the majority of children with visual deficits incurred posterior cortex and white matter injury, some infants with severe occipital injuries did not show signs of vision problems. Visual deficits included strabismus (2 of 34), visual field defects (2 of 34), cortical visual impairment (2 of 34), abnormal visual attention and tracking (1 of 34) and difficulties with visuo-spatial activities (1 of 34). Yalnizoglu et al. reported that only 4 of 10 children who suffered either occipital or occipito-parietal brain injury developed visual impairment [21]. Finally, a report by Karimdazeh et al of 27 children with history of symptomatic NH demonstrated that 12 of the 22 children who had occipital and parieto-occipital involvement on neuroimaging developed vision loss when assessed at the mean age of 3.5 years [23].

In summary, evidence for a direct and specific effect of NH on the integrity of the cortical and white matter pathways involved in vision is mixed. There also appears to be limited association between the presence of posterior brain injury and later visual function in studies of infants who experienced NH. At least three non-mutually exclusive explanations could account for this dissociation. Firstly, although the
methods used for visual assessment are typically not described, the testing was often conducted at a young age when accurate assessment of visual function is challenging [30]. Hu et al. demonstrated that even VEP measurements are difficult to interpret in neonates, showing that although all 15 infants with NH and posterior brain injury tested had abnormal VEP waveforms, 6 of 11 healthy control infants also had abnormal VEP findings [31]. Due to the difficulty in measuring visual function in infants, higher-level deficits such as agnosia resulting from damage to extrastriate brain areas as well as more subtle visual field or contrast sensitivity losses may not have been evident in studies to date. Providing some support for this theory are reports that experimentally induced hypoglycaemia (maintaining a blood glucose concentration of 2.5 mmol/L for 1 hour) in healthy adults does not affect clinical measures of visual acuity or stereopsis, but does impact on spatial contrast sensitivity and neuropsychological tests targeting higher-level visual processing and attention [32].

Secondly, NH may be associated with brain injury early in life, but the visual cortex is highly plastic during infancy and early childhood. It is conceivable that neural plasticity allows the remaining visual areas to compensate for minor brain injuries associated with NH [33]. Furthermore, both diffusion and structural MR data suggest that recovery of occipital regions from the effects of NH is possible over a period of weeks or months, indicating that NH may not permanently damage the occipital lobe in all cases [20,34].

Thirdly, deficits in vision resulting from early disruption to the visual system may not become apparent until later in development. Due to a lack of studies involving older
children, it is not known whether abnormal visual cortex function early in development can result abnormal visual development later in life.

**Prospective studies of neonatal hypoglycaemia and vision**

The majority of the studies described above have used retrospective case series designs to investigate the effect of NH on the eye and brain. However, a recent prospective follow-up study of 404 2-year-old children born at risk of NH, the Children with Hypoglycaemia and their Later Development (CHYLD) Study [4], has provided new data on the effects of mild to moderate treated NH on visual development. These infants underwent a detailed ophthalmic vision screening (visual acuity, stereopsis, red reflex, eye alignment, refractive error) and a measurement of global motion perception, a function of the dorsal visual cortical processing stream that may be particularly vulnerable to neurodevelopmental risk factors [35]. Two composite scores were generated, relating specifically to vision. The first was a vision impairment score that captured ocular and vision problems. The second was a refractive error score that captured clinically significant refractive error (hyperopia ≥ +4.00D, myopia ≤ -1.00D, and astigmatism ≤ -1.50D in any axis and anisometropia ≥ 3.00D). Global motion perception was measured using a motion coherence task, which assessed the ability to tolerate noise in an otherwise coherently moving dot field (a motion coherence threshold) [36].

Of the 404 children assessed, 216 experienced NH. Of the children who experienced NH, 152 (70%) had mild to moderate NH (blood glucose concentration of 2 to 2.6 mmol/L) and 64 (30%) had at least one severe episode of NH (blood glucose concentration < 2 mmol/L). No differences in vision impairment, refractive error or
global motion perception were found between the children who did and did not experience NH, suggesting that short periods of primarily mild to moderate NH do not affect visual development at age 2 years.

The prevalence of clinically significant refractive error within the cohort was 8% for the hypoglycaemic group and 11% for the non-hypoglycaemic group [4]. This rate was slightly higher than one of the previous NH studies that included refractive error measurements (2%) [6] and considerably lower than the other (22%) [23]. It should be noted that a non-cycloplegic refraction was conducted in the CHYLD study participants [4] that could have underestimated the prevalence of refractive error. Furthermore, all of the children enrolled in the CHYLD study who experienced NH were treated with the goal of keeping blood glucose concentrations ≥ 2.6mmol/L. Therefore, the hypoglycaemia experienced was generally mild to moderate (2 mmol/L to 2.6 mmol/L), unlike the majority of previous studies that included children who experienced severe hypoglycaemia (< 2 mmol/L). None of the children who experienced hypoglycaemia in the CHYLD study were blind (defined as visual acuity of ≥1.40 logarithm of minimum angle of resolution ~ 20/500 Snellen equivalent), unlike some previous studies [20, 21]. It is possible that effective treatment as soon as children were diagnosed with NH may have reduced the potential impact of NH on visual function. Results from a second follow-up of the CHYLD study at 4.5 years of age are awaited.

Conclusion
Current evidence suggests that severe and prolonged NH can be associated with injury of brain areas involved in visual processing, although the effect of these injuries on later visual function is currently unclear. This may in part be due to the difficulty of testing vision in young children. Furthermore, the fact that NH is frequently accompanied by co-morbid conditions that can also impair neurological function complicates interpretation of the case-series and case-review studies that constitute much of the current literature. Follow-up studies of randomized trials may help to isolate the effects of NH from those of other related conditions. At present, there are no consistently reported effects of severe NH on ocular development or eye alignment. Further, treated mild-moderate NH does not appear to affect visual function at 2 years of age [4]. However, the effects of abnormal visual experience early in life may only become apparent in late to middle childhood. It remains to be seen whether mild-moderate NH has an impact on visual function after preschool age.

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