Uitnodiging

Voor het bijwonen van de openbare verdediging van het proefschrift

VISUAL IMPRINTS OF VERY PRETERM BIRTH

Evidence for cerebral visual impairments in very preterm born children

op vrijdag 30 oktober 2015 om 11.45 uur

in de aula van de Vrije Universiteit, De Boelelaan 1105 te Amsterdam

Aansluitend bent u van harte welkom op de receptie

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CHAPTER 1

GENERAL INTRODUCTION
VISUAL IMPAIRMENT IN CHILDREN

According to the World Health Organization (WHO), visual impairment is defined as visual acuity less than 0.3 (spatial resolution >3 arc minutes) or visual field smaller than 30 degrees,\(^1\) equaling a more than three- to fourfold reduction of normal vision. The incidence of visual impairment in children is much lower than in adults and varies considerably across continents and regions due to differences in medical care.\(^2\) Existing prevalence numbers indicate blindness in 0.1 to 0.41 per 1000 children and severe visual impairment in 0.34 to 0.5 per 1000 children, across European countries.\(^3\) At present, registries for visually impaired and blind children in Western Europe and the United States indicate that cerebral visual impairment (CVI) is among the major causes of visual impairment in children, accompanied by retinal disorders, optic nerve hypoplasia and atrophy, and structural ocular pathology.\(^4\)-\(^7\)

CEREBRAL VISUAL IMPAIRMENT

The earliest studies of cortical blindness in young children date back to 1962, reporting cases of blindness following cardiac arrest and intracranial tumor resection.\(^8,9\) In subsequent reports, visual impairment predominantly results from perinatal hypoxic/ischemic encephalopathy.\(^10,11\) These early studies describe visual impairments ranging from complete blindness to “significant residual vision”, and noticed that most types of visual impairment met neither conventional criteria for visual impairment because of intact eyes, nor criteria for cortical blindness (i.e. absent vision with intact pupillary responses) because of some residual vision.\(^10,12-14\) Driven by the need for adequate diagnostic criteria for these severely visual impaired children, a first shift was seen in expanding the criteria for cortical blindness. In this shift, residual visual abilities were included and the disorder was renamed into cortical visual impairment.\(^12,14\) Similar to visual impairment resulting from ocular disease, cortical visual impairment initially referred to “lower order” visual sensory impairment only, such as reduced visual acuity and visual field defects. Furthermore, neurological as well as combined cerebral and ophthalmic pathology was found in the majority of children with CVI,\(^15\) indicating that CVI frequently co-occurs with cerebral palsy and neuro-developmental disorders.

Studies into problematic “higher order” visual perceptive functioning in children were also initiated since the 1960’s and report visual perceptive and visual-motor dysfunctions as important explanatory factors of the handicaps of these children.\(^16\) This study might have been the first move to recognize the importance of visual perceptive and visual-motor integration functioning in neurodevelopmental assessment. Since then, several authors
have described conceptual frameworks of CVI, including its etiology and diagnosis, with some of them incorporating visual perceptive dysfunctions into the defining criteria of CVI. Initially, Northern American groups restricted the definition of CVI to visual sensory deficits due to neurological abnormalities,17 thereby strictly following criteria for visual impairment due to ocular disease. The European literature, in contrast, classified visual sensory as well as perceptive deficits due to a range of neurological conditions as CVI.18 The inclusion visual perceptive deficits could be perceived as a second shift in expanding the defining criteria of CVI.

The most recent perspectives on CVI acknowledge that CVI occurs along a continuum of visual dysfunctions, narrowing the former gap between American and European literature.19 CVI includes visual dysfunctions associated with damage to any part of the visual brain system: optic nerves, optic radiation, primary visual cortex or visual association cortices,20 thereby excluding ocular and retinal pathology. Hypoxic-ischemic injury and inflammatory events including meningitis and encephalitis are recognized as leading causes of CVI in children,21,22 including subsequent periventricular white matter damage and hydrocephalus.23 The resulting spectrum of visual impairments includes deficits in any of the domains of oculomotor visual sensory, visual perceptive and/or visual-motor functioning, which are not mutually exclusive.24 Some deficits in visual attention have been recognized as additional explanatory factors for visual difficulties in children without damage to the cerebral visual pathways, but have not been included into the defining criteria for CVI so far.20 Furthermore, elaborating on the idea that CVI interferes with functioning in daily life, questionnaires assessing behavioral features of CVI have been introduced, aiming to assist in diagnostic assessment of children with CVI.25-27

In this thesis, CVI is defined in terms of visual deficits of any likely cerebral cause, thereby including a wide range of oculomotor, visual sensory and visual perceptive deficits of known neurological underpinnings, and excluding visual deficits due to optical abnormalities. Very preterm birth has been recognized as one of the major causes of CVI, because the accompanying hypoxic-ischemic injury and inflammatory events are a serious threat to the developing central nervous system including the visual pathways.22,28 Particularly, frequently occurring periventricular white matter disease is associated with visual-spatial perceptive dysfunctions.29

**Preterm Birth**

Preterm birth is defined as labor before 37 weeks of pregnancy. The WHO differentiates between late preterm birth (32-37 weeks of gestation), very preterm birth (28-32 weeks of gestation) and extremely preterm birth (<28 weeks of gestation).30 Preterm birth is a
relatively common complication of pregnancy that occurs on average in 11% of all live births worldwide, ranging from about 5% in several European countries to as high as 18% in some African countries, and 7% in the Netherlands.\textsuperscript{31} Risk factors associated with preterm birth are uterine abnormalities, multiple pregnancies, spontaneous preterm labor, premature rupture of the membranes, infections and preterm delivery for maternal or fetal indications, especially in case of hypertensive complications of pregnancy and placental insufficiency, which induce labor or require delivery by cesarean section. In addition, unfavorable socio-economic factors are associated with preterm birth.\textsuperscript{32}

This thesis focusses on children that were born very preterm or with very low birth weight (<1500 gram), which occurs in 1.3% of pregnancies in the Netherlands.\textsuperscript{33} Mortality as well as severe developmental disabilities following very preterm birth have considerably decreased over the past decades, due to advances in neonatal medical care.\textsuperscript{33,34} Despite these advances, very preterm born infants are vulnerable to the adverse effects of the untimely change to the extra-uterine environment. Combined effects of circulatory, respiratory, immunogenic and metabolic factors play a role in the causation of brain injury in very preterm infants, including intraventricular hemorrhages (IVH) and periventricular leucomalacia (PVL).\textsuperscript{35} The rate and severity of both IVH and PVL vary considerably, ranging from about 5% of severe, mostly focal, injury to as high as 50% of mild, diffusely scattered, white matter loss.\textsuperscript{35} These injuries adversely impact on neural migration, axonal outgrowth and myelination that specifically occur during the third trimester of gestation, thereby critically disturbing neural connectivity and leading to reduced cerebral grey and white matter volumes in childhood and adolescence.\textsuperscript{36} As a consequence, combinations of less severe adverse neurodevelopmental outcome across multiple domains of functioning are highly prevalent among very preterm born children that survive the neonatal period.\textsuperscript{37,38}

**VISUAL CONSEQUENCES OF VERY PRETERM BIRTH**

Visual development of very preterm born children is at risk for the adverse events associated with preterm birth that can hit multiple parts of the developing visual system. Retinopathy of prematurity (ROP) is a leading cause of visual impairment and blindness following preterm birth.\textsuperscript{39} ROP is caused by disturbances in vasoproliferation, due to antenatal as well as postnatal inflammatory and infectious events that increase the risk of retinal detachment and, in severe stages, can even cause severe visual impairment or blindness.\textsuperscript{40} Fortunately, the incidence of ROP has sharply decreased over the past decade: from 41% to 23% for all stages, and from 3% to 1% for severe stages.\textsuperscript{41} However, even very preterm children without ROP have less favorable visual outcome than term born controls.\textsuperscript{42} Besides impacting on ocular development, the adverse effects of preterm
birth also impact on visual functioning when the integrity of the cerebral visual pathways are affected.\(^43\) These pathways emerge from the retina and include the optic nerves and optic radiation, connecting the thalamic nuclei with the occipital visual cortex. In addition, complex and interconnected neural networks are involved in processing of visual information, serving recognition and visual-spatial analysis as well as visual-motor action, and are located in occipital-inferior temporal and occipital-parietal-prefrontal areas, respectively.\(^44,45\)

A wide variety of visual dysfunctions in very preterm children is found. In addition to increased rates of refractive error,\(^46\) large cohort studies have shown increased rates of oculomotor as well as visual sensory deficits in very preterm children\(^47-49\) and adolescents.\(^42,50-52\) These deficits include strabismus, reduced visual acuity, reduced contrast sensitivity and reduced stereovision. In contrast to the robust findings for ophthalmic outcome including oculomotor and visual sensory functioning, visual perceptive functioning and the ability to use visual information to guide motor behavior, referred to as visual-motor integration, have been studied less consistently and studies show great variability in samples studied, measures used, and concomitant outcomes. For instance, some studies that employed composite measures of visual perceptive functioning in very preterm children report medium-sized differences between very preterm children and term controls,\(^53,54\) whereas another study did not find these differences.\(^49\) Measures of visual-spatial perception, such as tests that require perception of line orientation, have identified medium to large-sized dysfunctions in visual-spatial abilities of extremely preterm and very preterm born children.\(^55-57\) Reported visual-motor integration problems vary from large-sized\(^57,58\) to small-sized and non-significant\(^59,60\) differences between very preterm children and their term born peers. Nonetheless, impairments in these “higher order” domains of visual functioning are associated with problems in adaptive functioning. Adaptive functioning refers to the ability to effectively interact with the environment, for example emotional and behavioral responses as well as academic achievement. For instance, weaker fine and gross motor skills,\(^47,48,50,51,61\) and academic underachievement\(^62,63\) in VLBW children are associated with visual perceptive dysfunctions. In addition, difficulties in visual perceptive abilities and visual-motor integration, substantially affect adaptive abilities including motor skills such as handwriting.\(^50,62\) Given the inconsistencies in methodology and findings between studies so far, a comprehensive overview integrating the results of studies into visual perceptive and visual-motor integration functioning of very preterm born children is urgently needed to characterize dysfunctions of VP/VLBW children in these domains. Furthermore, such an overview may aid studies tapping into the wide range of problems associated with visual perceptive and visual-motor dysfunctions.
Although the wide variety of visual dysfunctions in very preterm born children becomes increasingly evident, studies providing a comprehensive overview of visual dysfunctions as well as their repercussions for adaptive functioning are scarce. For instance, most existing studies focus on isolated aspects of visual functioning, i.e. either “lower order” visual outcome including refractive, oculomotor and visual sensory status or “higher order” visual perceptive functioning thereby missing the opportunity to study a broad range of visual functions as well as their repercussions. Some of the measures used in visual perceptive assessment heavily rely on other processes such as motor coordination (e.g. when copying figures or posting coins/cards into a slot) or measures that tap into multiple aspects of visual functioning simultaneously (e.g. images containing small details, incomplete contours as well as rotated objects). In addition, it has been argued that studies could fail to detect visual perceptive deficits because of the narrow scope of visual perceptive assessments that most times lack measures of object and face recognition. Another limitation in the current literature concerns integrating the effects of attention deficits in visual assessments, although attention is a core factor underlying human behavior and neurocognitive functioning including vision. Attention has even been highlighted as important additional factor in visual assessment and in understanding of visual deficits, but no studies have systematically combined visual assessments with measures of attention. Strikingly, attention problems are very common among very preterm born children, impacting on behavioral as well as academic functioning. Yet another limitation is that little is known about the impact of visual deficits on the well-established dysfunctions in motor, intellectual as well as behavioral functioning of very preterm children. Some studies have tapped into behavioral consequences of visual dysfunctions by studying behavioral signs of CVI. However, these studies have selectively employed questionnaires addressing the presumed behavioral consequences of CVI thereby neglecting possible alternative sources of behavioral difficulties. In very preterm children, behavioral difficulties such as attention deficit hyperactivity disorder (ADHD) as well as internalizing and externalizing behavioral problems are frequently found and require adequate differentiation from vision-related behavioral signs.

**AIMS OF THIS THESIS**

The main aim of this thesis is to extend insight into visual development of very preterm born children, by providing a detailed picture of visual functioning and by investigating repercussions of deficits in visual functioning on intellectual, behavioral and motor functioning. Specifically, this thesis aims to:

1. provide a comprehensive profile of visual functioning in very preterm children by:
   a. clarifying previous heterogeneous findings on visual perceptive and visual-motor integration dysfunctions in very preterm born children using meta-analysis,
b. including “lower order” oculomotor and visual sensory as well as “higher order” visual perceptive measures, and

c. extending the profile of visual functioning with measures of visual attention and visual-motor performance.

Subsequent aims are to:

2. establish a definition of CVI using clear cut empirical criteria, based on visual assessment outcome and evaluate its validity, and

3. study repercussions of visual, attention and visual-motor deficits on motor performance.

SAMPLE AND STUDY DESIGN

To investigate these aims, a follow-up study was performed in very preterm born children that originally participated in a multi-center study on post-discharge intervention between 2003 and 2006 in Amsterdam, the Netherlands. In the initial randomized controlled trial, all infants that were born with a gestational age below 32 weeks and/or birth weight less than 1500 gram in any of the two level-III hospitals with neonatal intensive care facilities or in any of the five city hospitals of Amsterdam were eligible for participation. Exclusion criteria were severe congenital abnormalities, severe maternal physical or mental illness/problems, not mastering the Dutch language and unavailability of an interpreter, and participation in other trials on post discharge management.

The follow-up study consisted of two visits between 2009 and 2012. The first visit took place at the Academic Medical Center Amsterdam, where assessments of motor as well as intellectual functioning were conducted. The second visit was scheduled within two weeks after the first visit at the regional visual rehabilitation center of Royal Dutch Visio in Amsterdam and included an orthoptic examination as well as a comprehensive assessment of visual perceptive and visual attention functioning. Both examinations included well-established measures as well as some newly developed computerized tests. During both visits, parents completed questionnaires about their child’s behavioral functioning. One-hundred-thirty-six very preterm children of the original cohort participated in the follow-up study. In addition, a sample of 67 term born children was recruited to serve as a control group. Term controls were recruited from regular schools attended by the VLBW children and by contacting additional schools located in the same geographical area. Controls were required to be born after more than 37 weeks of gestation and with a birth weight of more than 2500 grams. Exclusion criteria were parent reported severe perinatal complications or illnesses that might interfere with normal brain development, and learning difficulties.
LAY-OUT OF THIS THESIS

Chapter 2 describes a systematic review and meta-analysis investigating the impact of very preterm birth on visual perceptive and visual-motor integration functioning from childhood to adolescence, and aiming to unravel whether specific visual perceptive dysfunctions are underlying the visual perceptive problems in these children. The inclusion of studies using motor-free measures of visual perceptive functioning only was directed at eliminating effects of motor-based perceptive assessments. The impact of very preterm birth on visual-motor integration functioning was charted using the most widely used assessment: the Beery visual-motor integration test. In addition, this meta-analysis explores the effects of gestational age, birth weight, age at assessment, intelligence, and year of birth on visual perceptive and visual-motor outcome.

A comprehensive profile of visual functioning as well as attention functioning is described in chapter 3 and chapter 4. Chapter 3 presents the profile of oculomotor, visual sensory and visual perceptive abilities of very preterm born children. In addition, associations between visual sensory and perceptive deficits are explored, thereby considering whether routine visual screening procedures that are restricted to visual sensory assessment are also sensitive to detect visual perceptive deficits. In Chapter 4, the outcomes of two newly adopted computerized measures to assess visual search and attention network efficiency are reported. These tasks provide the opportunity of a detailed evaluation of very preterm children’s attention abilities. Systematically manipulating stimulus organization and density in the visual search task and by measuring manual reaction time under various circumstances in the attention allowed us to clarify previously reported heterogenic findings of attention functioning in preterm children.

A functional and empirically driven approach to CVI is presented in chapter 5, aiming to provide clear diagnostic criteria for CVI and to contribute to clarity in the ongoing debate on the definition of CVI. Chapter 5 extends the results of the deficits in oculomotor, visual sensory and visual perceptive functioning presented in chapter 3 by classifying all cases presenting with any type of visual deficit as CVI, except when these deficits are resulting from optical defects (i.e. abnormalities in refractive status). This newly developed approach to CVI is validated in two steps: 1) against a behavioral measure of CVI, and 2) against measures of intellectual and behavioral functioning. In addition, studying behavioral signs of CVI as well as the wider array of behavioral difficulties in very preterm children provides the opportunity to elucidate potential overlaps between CVI and behavioral and emotional problems.
Finally, **chapter 6** relates the results of the oculomotor, visual sensory, visual perceptive as well as visual-motor integration assessments to motor functioning, thereby investigating whether the deficits obtained using the wide range of visual measures are underlying the frequently reported motor problems of very preterm children. In addition, this chapter analyses the additional predictive value of these visual deficits to the well-known predictive value of abnormal neurological outcome for motor performance.
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Preterm and Very Low-Birth-Weight Children


