Thesis for doctoral degree (Ph.D.) 2009

VISUAL FUNCTION IN VERY LOW BIRTH WEIGHT ADOLESCENTS

Kerstin Hellgren

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FIFTEEN-YEAR FOLLOW-UP OF CHILDREN IN SOUTHEAST SWEDEN

Kerstin Hellgren

Karolinska Institutet

From the DEPARTMENT OF CLINICAL NEUROSCIENCE

Karolinska Institutet, Stockholm, Sweden

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ISBN 978-91-7409-316-2

Printed by


www.reproprint.se
Gårdsvägen 4, 169 70 Solna

ABSTRACT

Background: Very low birth weight (VLBW ≤ 1500 g) carries an increased risk of visual and cognitive deficits. Long term follow-up studies are sparse. The associations between neural structure and visual and cognitive outcome need to be more fully explored.

Aims: To describe visual functions in adolescents with VLBW in comparison with a matched control group and to investigate associations with white matter damage of immaturity (WMDI), optic disc measurements and cognitive functions in the VLBW group.

Subjects (Papers I-III): A total of 86 VLBW children survived the neonatal period during a 15 months period in the southeast region of Sweden. Fifty-nine of those, and 55 term control infants, participated in the 15-year follow-up study. **(Paper IV):** A subgroup including 18 VLBW subjects and 29 control subjects participated.

Methods: Structural assessments included brain MRI, digital analysis of fundus photographs and cycloplegic refraction. Functional evaluations comprised best corrected visual acuity, stereo acuity, visual fields, ocular alignment, fixation behavior, cognitive visual problems and intellectual level.

Results: Twenty-eight percent of the VLBW subjects had WMDI. The mean neural retinal rim area was smaller - in normal sized optic discs - in the VLBW than in the control group ($p=0.018$). The VLBW adolescents had more tortuous retinal arterioles than the controls ($p<0.001$). Astigmatism was more frequent in the VLBW group (19%; $p=0.001$). Significant differences between the groups were found, to disadvantage of the VLBW subjects, regarding visual acuity, stereo acuity and visual fields. Ocular misalignment, including heterotropia and heterophoria, was more common in the VLBW group (22%; $p=0.004$). The VLBW subjects had more horizontal vergence instability than the control subjects ($p=0.035$). The structured history revealed higher rates of cognitive visual problems in the VLBW group, in particular within depth, simultaneous, spatial orientation and motion perception. Intelligence quotients including full scale IQ, verbal subtests and performance subtests were significantly lower in the VLBW group.

WMDI was significantly associated with visual field sub normality, myopia, ocular misalignment, vergence instability and cognitive visual problems. Subnormal results of performance subtests were associated with decreased visual and stereo acuity, ocular misalignment, vergence instability and cognitive visual problems.

Conclusion: This study confirms previous observations that adolescents with VLBW are at a disadvantage regarding visual and cognitive outcome compared with adolescents with normal birth weight. Adolescents with WMDI had more pronounced visual and cognitive dysfunction.

LIST OF PUBLICATIONS

I. Hellgren K, Hellström A, Jacobson L, Flodmark O, Wadsby M and Martin L. Visual and cerebral sequelae of very low birth weight in adolescents. *Archives of Disease in Childhood Fetal Neonatal Edition* 2007;92:F259-64

II. Hellgren K, Hellström A and Martin L. Visual fields and optic disc morphology in very low birthweight adolescents examined with magnetic resonance imaging of the brain. *Acta Ophthalmologica 2008 Sep 20 [Epub ahead of print]*

III. Hellgren K, Aring E, Jacobson L, Ygge J and Martin L. Visuo-spatial skills, ocular alignment and MRI findings in very low birth weight adolescents. *Journal of American Association for Pediatric Ophthalmology and Strabismus 2008 In press*

IV. Hellgren K, Han Y and Ygge J. Fixation behaviour in very low birth weight and control adolescents. *In manuscript*

CONTENTS

LIST OF ABBREVIATIONS

BW	Birth weight
CP	Cerebral palsy
CT	Computerized tomography
DTI	Diffusion tensor imaging
ELBW	Extremely low birth weight
FSIQ	Full scale intelligence quotient
GA	Gestational age
ITA	Index of tortuosity for arterioles
IVH	Intraventricular hemorrhage
LBW	Low birth weight
LGN	Lateral geniculate nuclei
MAR	Minimum angle of resolution
MHR	Mean hit rate
MRI	Magnetic resonance imaging
pD	Prism dioptre
PIQ	Performance intelligence quotient
PVL	Periventricular leukomalacia
RB	Rarebit perimetry
ROP	Retinopathy of prematurity
SD	Standard deviation
SE	Spherical equivalent
SGA	Small for gestational age
VA	Visual acuity
VF	Visual field
VIQ	Verbal intelligence quotient
VLBW	Very low birth weight
WISC	Wechsler intelligence scale for children
WMDI	White matter damage of immaturity

1 INTRODUCTION

1.1 BACKGROUND

Neonatal intensive care has undergone major advances during the last decades. Antenatal corticosteroids given to the mothers, surfactant treatment to the preterm neonates, assisted ventilation and advances in monitoring sick newborns are examples of successful treatment in the management of prematurity (Crowther et al 2007, Geary et al 2008). These factors have had a positive impact on the outcome of premature birth. Consequently the survival rate of preterms is constantly increasing (Horwood et al 1982, Fanaroff et al 2003). The developing neonatal nursing also leads to an increasing survival rate of very small, immature and sometimes sick infants (Rudanko et al 2003, Fanaroff et al 2007, Volpe 2009).

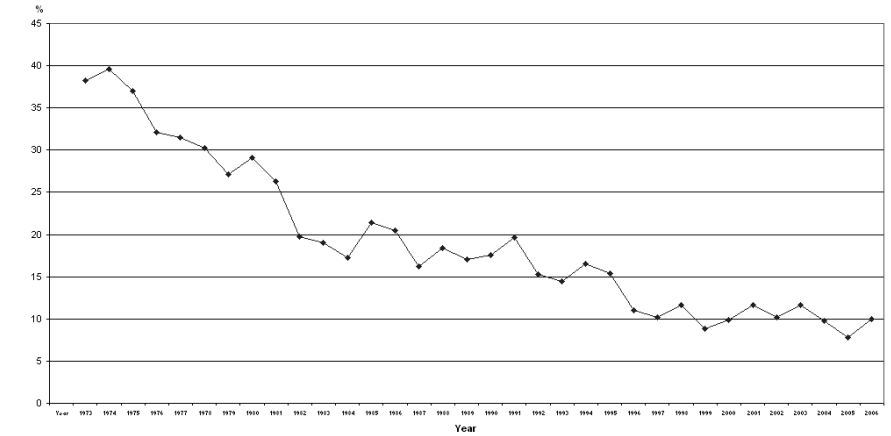


Figure 1. Neonatal mortality (0-28 days) in VLBW children 1973 – 2006 in Sweden. (Gäddlin 2008)

The incidence of children with very low birth weight (VLBW; ≤ 1500 g) in Sweden is slightly more than seven per 1000 born (Figure 1; The Swedish Medical Birth Registry 2008). Children with VLBW constitute a heterogeneous group of mostly premature children born small for gestational age (GA) or with a birth weight (BW) appropriate for GA. These infants run an increasing risk of developing motor impairment, i.e. cerebral palsy (CP) as well as cognitive and visual deficits (Escobar et al 1991, Darlow et al 1997a, 1997b, Botting et al 1998, Böhm et al 2002, O'Connor et al 2004).

The documentation of visual and ocular findings related to prematurity has paralleled the technical and medical development. In the 1940s a blinding disease was seen in premature infants. This feared ocular disease, initially called retrolental fibroplasia (Terry 1942), was thought to be caused by excessive oxygen supply. Advances in monitoring techniques of oxygen administration reduced the incidence of blindness in the 1970s (Gilbert 1997). In the 1980s a progressive retinal disease, retinopathy of prematurity (ROP) was defined and subsequently classified, and the etiology was found to be complex (Committee for the Classification of ROP 1984). Retrolental fibroplasia

was then identified as the end stage of ROP. As the number of surviving premature infants increased, ROP was considered a major public health problem. Major efforts were initiated for prevention and treatment of ROP, e.g. elaborate screening programs, improved treatment methods and follow-up schemes (CRYO-ROP group 1988, Hunter & Repka 1993, ETROP group 2003). Studies on visual function related to ROP and its treatment, were initiated (Dobson et al 1995, 2006, Fledelius 1996a, 1996b, Darlow et al 1997b, Larsson et al 2003, Davitt et al 2005, Fielder et al 2005, Palmer et al 2005).

However, with the increasing survival rate, long-term ophthalmologic complications became apparent, not always correlated to ROP, e.g. impaired visual acuity (VA), refractive errors and strabismus (Gallo & Lennerstrand 1991, Holmström et al 1999). Apart from ophthalmologic problems, reports on cerebral disorders linked to prematurity have been published (Hungerford et al 1986, Weisglas-Kuperus et al 1993, de Vries et al 1998). Autopsy findings of deceased preterm born infants described brain injuries with specific pattern and localization. Histological changes of the white matter adjacent to the brain ventricles in premature infants at post mortem were described in 1962 (Banker & Larroche) and named periventricular leukomalacia (PVL). The authors noted that the affected areas included the optic radiations and proposed that visual field defects would be a possible consequence of this damage. In the beginning of the 1980s acute cystic PVL and periventricular hemorrhages could be detected by means of brain ultrasonography (Levene et al 1981, Trounce et al 1986). During the last decade more sophisticated imaging techniques have disclosed a more complex pattern of periventricular lesions. Magnetic resonance imaging (MRI) has added new knowledge about the various white matter lesions in prematures. These lesions are categorized in four groups, comprising peri-/intra ventricular hemorrhages, periventricular hemorrhagic infarction, PVL and diffuse white matter injury (Volpe 2003) and are now labeled white matter damage of immaturity (WMDI). Spastic diplegia is a well known clinical sequel to WMDI (Hagberg et al 1996, Bax et al 2006). The neural correlate to this motor dysfunction is an interruption of the corticospinal tracts caused by the brain lesion (Krägeloh-Mann et al 1992, Staudt et al 2003). This functional deficit has attracted much attention from pediatric clinicians but visual defects, associated with WMDI, have only recently been studied. The visual field defects, which were predicted already by Banker & Larroche (1962), have been demonstrated, as well as reduced VA and increased frequency of strabismus (Jacobson et al 1996, Uggetti et al 1996, Cioni et al 1997, Jacobson et al 1998a, 2006). Furthermore, neuropsychological tests of children with WMDI have suggested impairment of a visual cognitive component, which could further complicate the visual experience of these children (Fazzi et al 1994, Jacobson et al 1996, Olsén et al 1998). Cognitive impairments are documented in individuals with WMDI (Olsén et al 1998, Soria-Pastor et al 2008) which is now considered to be of enormous public health importance because of the large number of prematurely born survivors (Volpe 2009).

Reduction of optic nerve fiber tissue, visualized by analysis of fundus photographs, has been demonstrated in prematurely born children, as well as increased tortuosity of retinal arterioles (Hellström et al 2002). An association between reduced optic nerve fiber tissue and WMDI has also been shown (Jacobson et al 1997, 2003).

Most of the reported data on visual outcome related to WMDI have been based on studies of premature children with neuroradiologically documented WMDI or clinical signs of brain lesions, i.e. cerebral palsy and/or cerebral visual impairment (Jacobson et al 1996, Cioni et al 1997, Fedrizzi et al 1998, Pennefather & Tin 2000, Ghasia et al

2008) Population-based studies of VLBW children including brain MRI and ophthalmologic outcome are sparse. Furthermore the majority of studies are carried out in children up to 10 -12 years of age, and only a few have followed the children up to adolescence (Powls et al 1997, Lindqvist et al 2007, Stephenson et al 2007, Lindqvist et al 2008).
This thesis will describe different aspects of visual and cognitive function in a population-based group of adolescents with VLBW in comparison with a matched control group. Associations between the functional outcome and WMDI as well as optic disc measurements in the VLBW group will be described and discussed.

1.2 STRUCTURE OF THE VISUAL SYSTEM

Visual pathways

The retino striate pathways

The retina, including the fovea constitutes the receptive area of the eye, and is neurobiologically a part of the central nervous system. There are different retinal neurons involved in the transmission of visual information. They include two kinds of photoreceptors, i.e. the cones and the rods, as well as the bipolar, the horizontal, the amacrine and the ganglion cells. The cones require high luminance (photopic conditions) for activation, while the rods are also activated under less illuminant (scotopic) conditions. The cones are numerous in the central retina and are the only photoreceptors found in the fovea. The retinal neural organization in the fovea is exceptional with high density of cones and ganglion cells, displaced outward from the fovea. The rods are much more numerous than the cones and dominate in the peripheral retina. The photoreceptors are connected by synapses to the bipolar cells, which transmit the visual signals further to the ganglion cells. Horizontal cells connect the photoreceptors to one another and amacrine cells connect ganglion cells likewise. There is overall convergence of receptors on ganglion cells, except in the fovea (Sjöstrand et al 1999). A receptive field is defined by the receptive retinal area of the receptors that mediate visual information through one ganglion cell. The axons of the ganglion cells merge to form the optic nerves. Upstream the nerves reach the chiasm, where the axons from the nasal part of the retina cross over and join the axons from the temporal retina of the other eye, to form the optic tracts. The tracts continue on each side of the brain stem. The axons in the optic tracts, now carrying information from one hemifield from the two eyes, terminate in the lateral geniculate nuclei (LGN) in the thalamus. A few of them reach the superior colliculi – see below. The synapses in the LGN mark the border between the anterior and the posterior visual pathways. Each LGN consists of six cell layers, organized so that the retinal receptor fields have a columnar representation through the six layers. The superior cell layers contain cells with small cell bodies and are called the parvocellular layers, whereas the inferior cell layers, containing cells with large cell bodies are called the magnocellular layers. The parvocells and magnocells mediate different modalities of visual information. From the LGN the optic radiations (also called the geniculostriate or geniculocalcarine tracts) carry visual information to the primary visual cortex located in the occipital lobes. Each

receptive field has a cortical representation and retinotopic maps in the visual cortex have been defined by means of functional brain MRI (Wandell et al 2007).

The retino-collicular pathway

Schneider (1969) proposed the existence of two separate visual systems within the human brain, carrying different modalities of visual information. The cortico-striate pathway, briefly described above, carries conscious visual information of identification and discrimination. He also suggested the existence of a tectal/collicular pathway, carrying unconscious spatial orienting visual information. This pathway passes through the superior colliculi into the brainstem, and never reaches the striate cortex. Schneider based this concept on comparisons of the effects on vision from brainstem versus cortical lesions in animals and humans. Subsequent case reports have suggested that the collicular visual system serves as the subconscious visual guidance for locomotion, responsible for travel vision (Jan et al 1986).

Intercortical pathways

Goodale & Milner (1992) opposed the theory, suggested by Schneider as above, that the visuo-spatial information was attributed only to the collicular pathway. They proposed that the visual global information was processed in the striate cortex and from there two mainly distinct pathways were carrying the primary visual information to associate cortex areas. They suggested that a ventral stream of projections to the infero-temporal cortex played the major role in the perceptual identification of objects, while a dorsal stream of projections to the posterior parietal cortex mediated information for visually guided movements and orientation in space. Several studies have confirmed this theory and it is now generally accepted although debated (Gunn et al 2002, Braddick et al 2003, Montfoort et al 2007). The analysis of motion and spatial orientation as well as the ability to differentiate details from an overall scene is suggested to take place in the parietal lobes (Mishkin & Ungerleider 1982, Haxby et al 1991, Valenza et al 2004). Visual attention and visual guidance of movements are also processes, presumed to be monitored from the parietal lobes (Goodale & Milner 1992, Battelli et al 2008). Visual memory, color vision and recognition of form and faces are suggested to be processed in the temporal lobes (Riesenhuber & Poggio 2002, Dutton 2003, Barton 2003). Cognitive visual function refers to combined results from this complex processing of visual information.

1.3 PREMATURITY & STRUCTURE OF THE VISUAL SYSTEM

The structural changes of the visual pathways related to prematurity are complex, involving various kinds of neural tissue, which may have been injured or altered during different developmental stages. The anatomical changes can be defined using imaging techniques. The structures described in this thesis include the cerebral lesions documented with standard MRI, optic disc and retinal vessel structure measured with digital analysis of fundus photographs and also cycloplegic refractive measurements.

1.3.1 Retinopathy of prematurity

ROP is a vascular disorder caused mainly by the immaturity of the infant and the retina. The exact mechanism behind the disease is enigmatic, but many interacting factors have been identified. The degree of prematurity is considered to be the major impact factor (Holmström et al 1998, Hussain et al 1999). Low BW and perinatal events such as pulmonary insufficiency requiring assisted ventilation, as well as shifting oxygen levels, neonatal infections and poor weight gain are other documented contributors (Cunningham et al 1995, Wallace et al 2000, Falciglia et al 2003). Recent studies have added deficient head growth and insufficient levels of insulin like growth factor (IGF) to the list of risk factors for developing ROP (Smith 2005, Löfqvist et al 2006). The nature of ROP is complex. Briefly it comprises a sudden arrest of the proceeding growth of retinal vessels. This growth of retinal vessels is not completed until 40 weeks GA under normal circumstances. In case of disease progression, pathological new vessels are developed and may induce traction of the retina and cause scarring or finally retinal detachment. The disease is described in terms of severity, stage 1 being the mildest form and stage 5 being the most severe and blinding stage due to total retinal detachment. The frequency of ROP of all stages is in the industrialized part of the world reported to be 10 - 40% in population-based VLBW studies (Holmström et al 1993, Haugen & Markestad 1997, Larsson et al 2002, Darlow et al 2003). Most ROP has regressed spontaneously by 39 weeks postmenstrual age (Fielder et al 1992) and at 40 weeks 75% of ROP has shown onset of involution (Repka et al 2000). However, about 10% of all ROP needs treatment to regress (Larsson et al 2002). Destruction of peripheral unvascularized retina by cryotherapy was previously the method of choice, but has been replaced by argon laser photocoagulation (Laser ROP group 1994). Studies suggest that laser treatment causes less refractive errors than cryo treatment (Connolly et al 2002). In spite of treatment some cases progress to retinal detachment and blindness and other cases of ROP heal with scarring and macular folds (cicatricial ROP) causing visual impairment. A recent study of infants born before 25 weeks GA showed a 33% frequency of visual impairment, due to ROP, in boys and 9% in girls (Jacobson et al 2008).

1.3.2 Brain injury in premature infants

Some aspects of neural development

To understand the brain lesion pattern associated with prematurity, the neurological and vascular development has to be taken into account. During the third trimester the "gross architecture" of the brain is established. Differentiation processes predominate including axon, dendrite and synapse formation and myelination (Krägeloh-Mann 2004). The periventricular white matter is particularly vulnerable at the beginning and middle of the third trimester, in particular between the 24^{th} and 34^{th} weeks GA. In this area run the posterior visual pathways and the corticospinal and other pathways. It also includes the germinal matrix, a highly cellular region from which cells migrate out during brain development. The germinal matrix is the source of both neurons and glial cells. It is visible with MRI up to around 32 weeks GA, along the margins of the lateral ventricles (Counsell et al 2002). Thereafter it probably regresses. Beginning of myelination of the white matter is visualized at 36 weeks GA (Counsell et al 2002).

However, unmyelinated white matter is the most prominent brain tissue class in the preterm infant at this age (Hüppi et al 1998). During the third trimester there is a rapid proliferation of oligodendrocytes in the periventricular white matter. These are the cells responsible for myelin formation in the central nervous system. The myelination proceeds after birth and is not completed before two years of age (Volpe 2001, Parazzini et al 2002).
At the beginning and middle of the third trimester the end capillaries from the cerebral arteries have not reached the periventricular white matter. The consequence is an extremely low blood flow in the white matter (Børch & Greisen 1998, Khwaja & Volpe 2008). The unmyelinated periventricular axons are thus located in a watershed area where oxygen is supplied only by diffusion. Furthermore, there are data suggesting that the cerebral auto regulation is not intact in premature infants (Soul et al 2007). Thus the premature brain is exposed to pressure passive circulation, and therefore extremely sensitive to changes in blood pressure. Hence the periventricular area is vulnerable to both shifting levels of oxygen supply (due to immature lungs) and to varying blood pressure, both of which the premature baby is exposed to in the extra uterine milieu. Decrease in oxygen supply and hypotension may cause ischemic lesions and increased blood pressure may induce hemorrhages. Infections, poor nutrition and steroids may also induce white matter damage (Volpe 2001).

Neuroimaging findings

The pattern of cerebral injury found in premature infants depends on the maturity of the brain at the time of the insult. When brain damage occurs during the beginning to mid third trimester, the lesions typically occur in the white matter (Hüppi et al 1998, Counsell et al 2003, Krägeloh-Mann 2004, Inder et al 2005). These changes of prenatal origin are less often seen in full-term children. Before the advent of imaging techniques, the diagnosis could only be made at autopsy. Indeed PVL is a histological diagnosis, seen as a softening of the white matter and focal cystic degeneration (Volpe 2001). In the beginning of the 1980s when ultrasonography was coming into use, the correlation between findings from this method and autopsy was documented (Hill et al 1982). Apart from PVL, peri- and intra-ventricular hemorrhages could be visualized. Ultrasonography is easily performed and is now routinely done in neonatal unites caring for very preterm babies. Yet, the method has clear limitations. First, the time of examination is limited to the neonatal period before the closure of the anterior fontanel, "the window" for the probe. As the myelination of the white matter is not completed until two years of age, abnormal or deficient myelination cannot be diagnosed. Second, ultrasonography has a low sensitivity for detection of non-cystic white matter damage (Consell et al 2003, Inder et al 2005). MRI is a non-invasive and non-ionising technique, shown to be safe and adequate in visualizing white matter damage (Flodmark et al 1989). There are four specific lesions described of the mainly unmyelinated tracts, or white matter. These comprise germinal matrix hemorrhage and/or intraventricular hemorrhage, periventricular hemorrhagic infarction, periventricular leukomalacia and diffuse white matter injury (Volpe 2003). Commonly, infants present with multiple lesions. The end-stage lesion is summarized by the term white matter damage of immaturity (WMDI), as already mentioned. A study of eight year old children with BW < 1750 g, documented a 32% incidence of PVL (Olsén et al 1997). Recent studies with conventional MRI have shown that non-cystic white matter injury, often accompanied with ventricular dilatation is much more common than cystic

white matter damage (Stewart et al 1999, Inder et al 2005). Grey matter abnormalities in the cortex or in the deep nuclei may accompany WMDI (Inder et al 1999). Conventional MRI can visualize focal lesions gliosis (scar tissue) and tissue loss, but quantification of myelination or brain volume is not possible with this technique. Recently developed volumetric MRI techniques have shown brain volume reduction in prematurely born children and reduced brain volumes in comparison with controls have been reported in VLBW adolescents (Abernethy et al 2002, Martinussen et al 2005). Diffusion tensor imaging is a new MRI technique that measures the size and number of myelinated axons in the white matter. Reduction of myelinated axons in the internal and external capsule, corpus callosum and superior fasciculus has been documented in VLBW adolescents, using this technique (Vangberg et al 2006).
Besides ROP and WMDI infants born very preterm run a risk of developing post-hemorrhagic hydrocephalus (Volpe 2001). The subsequent increased intracranial pressure adds to the threats against the anterior and posterior visual pathways in these individuals.

1.3.3 Ocular fundus abnormalities

The ocular fundus includes the retina with the fovea, the optic nerve and the retinal vessels and can be visualized directly by ophthalmoscopy. Pathology in the central nervous system may be reflected by abnormalities of the optic disc and the retinal vessels (Hellström 1999). Digital image analysis techniques of fundus photographs has made it possible to calculate the optic disc size and the tortuosity and the number of branching points of the retinal vessels (Strömland et al 1995).

The optic disc
The optic disc is the intraocular starting point of the optic nerve, visible by ophthalmoscopy. The optic nerve is growing rapidly during the third trimester, both with respect to length and width (Takayama et al 1991). Paradoxically the growth in volume parallels a genetically programmed nerve cell death, apoptosis. About two thirds of the axons in the optic nerve are lost from a peak density at around week 17 to adult levels at around week 30 GA (Provis et al 1985). The myelination of the optic nerve is completed around week 32 GA (Takayama et al 1991).
Optic nerve hypoplasia is a congenital anomaly. The term hypoplasia indicates a primary failure of development and growth of an immature structure. Optic nerve hypoplasia represents a reduced number of axons (Hotchkiss & Green 1979). The etiology remains unknown but optic nerve hypoplasia has been associated with teratogenic drugs, congenital infections and central nervous system abnormalities (Lambert et al 1987, Hoyt & Good 1992, Brodsky & Glasier 1993, Hellström 1999). The diagnosis may be difficult in mild cases. Furthermore the classic sign of a small underdeveloped optic disc, visualized by ophthalmoscopy, is not always present. Indeed Frisén and Holmegaard presented 30 years ago cases of optic nerve hypoplasia with normal optic disc size, but with defects in the retinal nerve fiber layer and corresponding visual field defects (Frisén & Holmegaard 1978). When the nerve fibers leave the eye through the lamina cribrosa (a roughly circular seivelike structure in the posterior wall of the bulb) they form the rim area in the optic disc. A previous population-based study of children born before 29 weeks GA demonstrated significantly smaller optic disc area and smaller rim area in the premature group than in

controls born at term (Hellström et al 2002). Preterm birth has been identified as a risk factor for optic nerve hypoplasia in visually impaired children (Tornqvist et al 2002).
A relationship between WMDI and optic nerve hypoplasia has been documented (Brodsky & Glasier 1993). The neurodevelopmental mechanism was suggested to be destruction of the optic radiations, due to WMDI, causing a transsynaptic retrograde degeneration of the optic nerve axons, leading to optic nerve hypoplasia. Morphometric studies on fundus photographs from preterm infants with WMDI have demonstrated different variants of optic nerve hypoplasia. One variant was manifested as normal sized optic discs with large cups (Jacobson et al 1997). The authors suggested that this appearance could be attributed to a cerebral lesion late in pregnancy, with secondary loss of optic nerve axons, but remaining dimensions of the supportive tissue due to less flexibility. This theory was supported by a subsequent study, in which timing, by means of neuroradiology, of the brain lesions and the optic disc dimensions were compared. Small optic discs were seen in preterm infants with brain lesions estimated as having occurred before 28 weeks of gestation, and normal sized discs with large cupping after 28 gestational weeks (Jacobson et al 2003). Optic nerve hypoplasia has also been associated with intraventricular hemorrhages in preterm infants (McLoone et al 2006).

Retinal vasculature

Abnormalities of the retinal vasculature may be identified with respect to number, tortuosity or diameter of the retinal vessels. Increased artery tortuosity has previously been documented in preterm children in association with ROP (Fielder et al 1992). In other studies increased persistent arterial tortuosity has been reported also in preterm subjects without history of ROP (Baum 1971, Hård et al 2000). As reported by Bracher, a marked increase in tortuosity of the central retinal arteries occurred in newborns exposed to hypoxia. The tortuosity seemed to be transitory in many cases and disappeared when the hypoxic distress was eliminated (Bracher 1982). Thus hypoxia is considered to be a prerequisite for abnormal retinal vascular pattern. The mechanism behind the increased tortuosity of the retinal arteries, associated with hypoxia is not known. Relaxation of the arteriolar muscles resulting in vessel elongation and abnormal tortuosity, as well as degeneration of astrocytes due to hypoxia has been proposed (Bracher 1982, Chan-Ling & Stone 1992). Growth hormones and angiogenic factors seem to play a crucial role in the retinal vascular architecture seen in preterm subjects too (Hellström et al 2002). There have been speculations and indications that the retinal vasculature noted in preterm individuals reflects similar changes in other organs, e.g. the kidneys. A study of 23-30 year old women born preterm and age-matched controls reported increased retinal arterial tortuosity and increased blood-pressure in the ex-preterm women compared to the controls (Kistner et al 2002). Increased blood-pressure in VLBW adolescents has also been documented (Pharoah et al 1998).

1.3.4 Refractive errors

The refraction of the eye depends on the relationship between the corneal curvature, the depth of the anterior chamber, the lens power and the axial length. The natural refractive state of a newborn infant is hyperopia and astigmatism (Saunders et al 1995). The hyperopia and astigmatism regress within the first years of life towards

emmetropia. The exact mechanism behind the emmetropisation process is not known. It is partly due to genetic factors but it is also probably centrally monitored, by a neuronal response to visual experience (Troilo 1992). There is reason to believe that the emmetropisation process is altered in ex-preterm individuals (Saunders et al 2002). Increased frequency of refractive errors in prematurely born children is reported in many studies (Darlow et al 1997b, O'Connor et al 2006). Myopia is reported in many studies as secondary to ROP, to cryo treatment and also to prematurity per se (Gallo & Lennerstrand 1991, Quinn et al 1998, Ricci 1999, Larsson et al 2003). Hyperopia and also astigmatism are also more frequent in prematurely born children (Larsson et al 2003). Myopic adults with a history of ROP have shorter bulb length and increased corneal curvature than myopic adults born at term (Baker & Tasman 2008). Reports on refractive errors in VLBW adolescents are sparse. One study reported similar refraction in 14- year old VLBW and control subjects (Lindqvist et al 2007). In adolescence myopia is documented in many healthy subjects born at term and there are reports of a 40% rate of myopia in 12-13 year old subjects (Villarreal et al 2000). It is noteworthy that the incidence of refractive errors is highly dependent on the methods used, i.e. the degree of cycloplegia, and the definition used. These parameters differ between studies and weaken comparisons.

1.4 PREMATURITY AND FUNCTION

1.4.1 Visual function

There are many modalities of visual function, measured in different ways. It stands to reason that the tools available do not measure all modalities. The most common measurement is visual acuity (VA), i.e. the capacity to discriminate / resolve details with high contrast and luminance. This quality of vision is corresponding to the fovea function and the foveo-cortical pathways. The visual field is dependent on the peripheral retina and the retino-cortical pathways. Stereo acuity is a measurement of binocular spatial resolution. Color vision, contrast sensitivity and motion detection are examples of other visual functions, not studied in this thesis.

Visual acuity
Human infants are born with low VA compared to adults (Dobson & Teller 1978). The fovea is not matured until several months after term birth (Hendrickson 1992). The development of VA proceeds during childhood and is considered to have finished by 8-10 years of age (Daw 1998). There is reason to believe that the VA development is not completed until adolescence or early adulthood (Frisén & Frisén 1981, Ohlsson & Villarreal 2005). A successful visual development requires a good quality of visual stimuli. Uncorrected refractive errors or blurred optic media preclude a normal development and can result in persistent subnormal VA, i.e. amblyopia (Hubel & Wiesel 1963). Amblyopia is most often monocular due to strabismus or anisometropia. The mechanism is not entirely known, but is probably the cortical result of a suppression of visual input to the visual cortex from the strabismic or ametropic eye, in order to avoid diplopia and confusion. The foveal function is dependent on the retinal photoreceptors receiving and the neurons carrying the information. Damage to these

structures impairs the VA. Prematurity carries a risk of injury to the retina and the visual pathways. Cicatricial ROP can cause injury to the fovea resulting in decreased VA. The effect of less severe ROP on the photoreceptors has been studied with neurophysiologic examinations using electroretinogram (ERG) by Fulton and co-workers (2008). These studies have shown that the cones are more resistant to the ROP disease process than the rods (Fulton et al 2008). The posterior pathways are vulnerable to ischemic and hemorrhagic lesions, associated with prematurity. The associations will be discussed below. There is convincing data showing that VA is reduced in preterm children (Gallo & Lennerstrand 1991, Darlow et al 1997b, Hård et al 2000, Cooke et al 2004). The reduced VA seems to persist according to longer follow-up studies (Powls et al 1997, O'Connor et al 2004, Larsson et al 2005, Lindqvist et al 2007). Visual impairment according to the criterion of the World Health Organization (2007) has been reported in rates between 1.8 % and 7 % in premature-born children (McGinnity & Bryars 1992, Tuppurainen et al 1993, Darlow et al 1997b, Hård et al 2000, Larsson et al 2005). Visual impairment has shown to be commonly accompanied by cerebral dysfunction, e.g. CP, mental retardation and epilepsy in preterm subjects (Rudanko et al 2003).

Reduced grating acuity has been documented in preterm infants with WMDI, diagnosed with ultrasonography (Eken et al 1994, van den Hout et al 1998). Jacobson and co-workers have reported reduced VA in children with neuroradiologically verified WMDI (Jacobson et al 1996). The neuronal correlate to impaired VA is suggested to be lesions involving the inferior posterior periventricular areas (Krägeloh-Mann et al 1999). Visual crowding is a phenomenon described in young children with cerebral visual impairment of various etiologies (Jan & Groenveld 1993). It refers to an inability to resolve linear optotypes, while single optotypes of the same size may be identified. Crowding has also been described in preterm children with moderate to severe WMDI (Pike et al 1994, Jacobson et al 1996).

Visual fields

While testing of VA corresponds to the foveal function the assessment of the visual field (VF) corresponds to the retina – and retino-cortical channels - surrounding the fovea. A cortical retinotopic map has been shown to correspond to the retinal receptive fields (Wandell et al 2007). The visual fields in pre-school children are often assessed by manual, kinetic Goldmann perimetry. The maintained interaction, required with this method, between the investigator and the child examined, makes it suitable for young individuals. With this method peripheral constrictions of the visual fields have been demonstrated in prematures with ROP treated with cryo therapy or laser ablation (Quinn et al 1996, Larsson et al 2004, McLoone et al 2007). Another large study suggested that most of the deficit was related to severe ROP rather than to the cryotherapy/laser ablation (CRYO-ROP group 2001). Static, computerized perimetry techniques are considered to be more accurate and more suitable for detecting subtle central VF defects. However the sensitivity between the different techniques differs and due to different stimuli properties (type, size and intensity) the comparison between different studies may be difficult. In a study of 11-year old VLBW subjects Larsson and co-workers found increased resolution thresholds, indicating decreased sensitivity, in the central 30 degree VF, unrelated to ROP (Larsson et al 2004). This sensitivity reduction could not be confirmed in a recent study by Lindqvist et al (2007), which examined VLBW adolescents using a differential light threshold method. O'Connor

and co-workers, using the Damato Campimeter (an oculokinetic perimetry chart able to detect major visual field defects) did not find any differences between adolescents with BW<1750g and controls (O'Connor et al 2004). Visual field restriction has been documented in small children with WMDI (Cioni et al 1997). Inferior visual field defects have been documented with Goldmann technique in children with WMDI (Jacobson et al 1996, 2006). These defects represent bilateral homonymous quadrant dysopsia or, less often, anopsia. In children with unilateral or asymmetric WMDI, homonymous visual field defects have been found (Jacobson et al 1996). Dutton and co-workers have reported inferior visual field impairment demonstrated with confrontation techniques in children with cerebral visual impairment (Dutton et al 2004). Posterior superior periventricular white matter is commonly affected by WMDI and this tissue sub serves the inferior visual fields (Edmond & Foroozan 2006).

Stereo acuity

Stereo acuity, i.e. the relative localization of visual objects in depth, can occur only in binocular vision. Specific binocular neurons in the visual cortex induce stereo vision when activated with almost identical but disparate images on to the foveae of the two eyes (Hubel & Wiesel 1970). Stereopsis has a sudden onset at around three months of age and thereafter shows a rapid development up to six months of age, and continues to delevelop more slowly until reaching adult values around the age of five to six years in almost all healthy, term infants (Hong & Park 2008). Compared to the development of VA, the time course for the development of stereo acuity is extremely rapid. Convergence is known to be fairly well developed by the age of two months. Previous studies on healthy neonates suggest that convergence stability may be a necessary but is not a sufficient condition for the onset of stereopsis (Held et al 1980, Birch et al 1982).

Stereo vision is not the only means for spatial orientation. Monocular cues, such as head movements, inducing motion parallax, linear perspectives, overlay of contours and distributon of shadows, add to the depth perception. These are compensatory strategies aquired by visual experience. The role of high quality stereo vision in visuo-spatial perception and visuo-motor skills is not fully understood. Stereo acuity is a relative function that can be measured (in seconds of arc) and categorized (as present or absent) with stereograms. There are diverging reports on the normal stereo acuity in different ages. Jiménez and co-workers documented unvaryingly a mean stereo acuity of 25 seconds of arc in ages from 6 to 12 years (Jiménez et al 2004). Aring and co-workers reported increased stereo acuity with age in 4 to 15 year-old control children (Aring et al 2005). Stereo acuity is reported to be the same at distance and near under normal viewing conditions (Wong et al 2002).

Many studies have reported decreased stereo acuity in VLBW children compared to controls (Dowdeswell et al 1995, Jongmans et al 1996, Hård et al 2000, O'Connor et al 2002, Holmström et al 2006, Lindqvist et al 2008). The results of association analysis with strabismus vary (O'Connor et al 2002, Holmström et al 2006). There is sparse documentation on stereo acuity and WMDI, and almost always reported secondary to strabismus.

1.4.2 Oculomotor control

Oculomotor control is essential to achieve optimal visual input. Therefore ocular alignment and fixation stability was evaluated in the current study.

Ocular alignment

Proper alignment of the eyes is guaranteed by a normally functioning sensory and motor fusion mechanism. Heterotropia, or manifest strabismus, is the condition when such fusion mechanism is absent or deficient. The result can be a convergent, divergent or vertical strabismus defined as esotropia, exotropia and hypo/hypertropia respectively. Convergence might also be a physiologic mechanism to permit binocular vision at near. Convergence is physiologically closely related to accommodation, which is the term used for defining the required increase of the lens curvature, executed by the circular ciliary muscle, to produce clear sight at near. In case of hyperopia, accommodation is continuously sustained in order to produce clear vision also at distance. As convergence physiologically parallels accommodation hyperopia thus results in maintained convergence which in some individuals may end up in convergent manifest strabismus, so called refractive esotropia. This kind of strabismus may promptly disappear when adequate correction is used (von Noorden & Campos 2002). Neurologically convergence is suggested to be monitored from the superior colliculi and adjacent structures in the midbrain. In addition the cerebellum and multiple cortical areas are considered to contribute to vergence eye movements (Leigh & Zee 2006). The neuronal correlate or the mechanism behind strabismus is not known. Heterophoria is a latent deviation of the visual axes of the eyes, manifested only in the absence of all stimuli to fusion (Schroeder et al 1996). Latent strabismus can be manifest at periods and is then called intermittent heterotropia. Heterophoria, i.e. latent strabismus is a common finding in the normal population. Physiological heterophoria is defined as an interocular angle within 2 prism dioptres (pD) of esophoria and 4 pD of exophoria at distance (Moses RA 1970). Lindqvist and co-workers found similar ranges in their control group of 14-year old healthy subjects (Lindqvist et al 2008).

Many studies have reported increased rates of strabismus in VLBW children of different ages (McGinnity & Halliday 1993, Pott et al 1995, Fledelius 1996b, Pennefather et al 1999, Holmström et al 1999, 2006, Hård et al 2000). However the distinction between heterotropia and heterophoria has not always been clear. Most studies have presented heterotropia only. Furthermore, most of the previous studies have been performed in young populations and in only a few of them the follow-up periods have extended past 10 years of age (Powls et al 1997, O'Connor et al 2002, Lindqvist et al 2008). Strabismus has been documented in children with moderate to severe WMDI (Jacobson et al 1998a). It has also been reported in high frequencies in children with myelomeningocele and hydrocephalus (Lennerstrand et al 1990, Caines et al 2007, Aring et al 2007a). Intraventricular hemorrhage has been reported to be associated with strabismus in VLBW children (McGinnity & Halliday 1993). Spastic diplegia is causally linked to WMDI (Hagberg et al 1996, Bax et al 2006) and the association between strabismus and spastic diplegia has been documented in several studies (Kozeis et al 2007, Ghasia et al 2008).

Visual fixation

The ability to maintain a steady binocular fixation is one of several aspects of good visual function. Small amplitude eye movements (amplitudes less than 0.3 degs) during fixation have been documented in healthy subjects. These involuntary fixation eye movements are considered to prevent adaptation of the retinal receptors to an unchanging visual scene (Ditchburn 1980, Martinez-Conde et al 2004, 2006, Leigh & Zee 2006). However, steady fixation requires suppression of other ocular motor activities such as the vestibular ocular reflex. Steady tonic vergence is required to maintain binocular single vision at any given distance. The suppression processing and vergence accuracy are probably proficiencies that develop in part in childhood (Aslin 1977, Kowler & Martins 1982, von Hofsten & Rosander 1996, Bucci & Kapoula 2006). Ygge and co-workers studied fixation stability in children aged 4 to 15 years using the infrared reflection technique and documented increased fixation stability with increasing age (Ygge et al 2005, Aring et al 2007b). Vergence stability was not accounted for. The neural correlate or the consequences of unsteady fixation behavior or unstable vergence capacity are not known. Impaired fixation stability has been demonstrated in children with severe WMDI (Salati et al 2002). Nystagmus is a common finding among children with cerebral visual impairment due to WMDI as well as other brain lesions (Jacobson et al 1998, Salati et al 2002).

1.4.3 Cognitive function

Intellectual level

There are several methods to measure cognitive proficiencies in children. Many of them include assessments of verbal skills on the one hand and visuo-spatial, so called performance skills on the other. The tests are often time-consuming and are not used for screening purposes. Different tests are used for different age groups, and the results are often given in mean intelligence quotients (IQ), normal ranges being 100±15 IQ units (Wechsler 1999). There is convincing data showing that VLBW children run a high risk for cognitive impairment and educational under-achievement (Rickards et al 1988, 2001, Botting et al 1998, Horwood et al 1998, Gäddlin et al 2008a). A meta analysis of studies of 5 to 14 year old VLBW children disclosed mean differences between 7 and 23 IQ units, 95% CI 9.2-12.5 (Bhutta et al 2002). There are data suggesting that the cognitive deficits in VLBW children increase from childhood to adolescence. It is not clear whether this finding represents a genuine deterioration in cognitive function or is an expression of pre-existing pathology in an increasingly complex environment (Hack et al 1995, O'Brien et al 2004).

Cognitive visual function

Several studies, as presented below, have reported unusual cognitive profiles assessed with Wechsler Intelligence Scale for Children-III (WISC-III) in prematurely born children. The consequent finding is that the performance scores are more deficient than the verbal. In VLBW children, including children with normal IQ these findings were documented by Hunt and co-workers (1988). The investigators also found visuo-motor skills particularly affected. Similar findings were documented by Herrgård and co-workers in prematurely born children (Herrgård et al 1993). In visually impaired children with WMDI the same cognitive profiles were reported by Jacobson and co-workers (Jacobson et al 1996). A population-based Finnish study of children with BW

below 1750 g suggested that the prematurely born children had lower cognitive abilities than the controls, in particular lower visuo-spatial ability, associated to PVL (Olsén et al 1998). Hård and co-workers reported impaired visual perceptual skills in five to nine year old children born before 29 weeks GA compared to term controls (Hård et al 2000). The difference in visual perceptual performance between the groups increased with age. In the same population Gabrielson et al documented a large variability in performance intelligence quotient (PIQ), not related to verbal intelligence quotient (VIQ; Gabrielson et al 2002). Although there are many tests for visuo-spatial and visuo-motor skills, there is no clinical test designed for detection of impaired dorsal and ventral stream mediated functions.

Structured history taking

Dutton defined five categories of cognitive visual disorders, found in children with visual impairment, secondary to cerebral lesions. The five categories involved impairment of recognition, orientation, depth perception, perception of movement and simultaneous perception (Dutton et al 1996). Depth and simultaneous perception, as well as perception of movements and spatial orientation are suggested to be processed in the parietal lobe, hence mediated through the dorsal stream, as previously mentioned. Recognition is accordingly suggested to be processed in the temporal lobes, mediated by the ventral stream (Dutton 2003). Dutton and co-workers used a questionnaire organized as a structured history to identify the cognitive visual problems. The structured history taking has been used as a tool to assess cognitive visual problems/dysfunction in children with hydrocephalus and in prematures with various signs of cerebral lesions. A high frequency of cognitive visual problems has thus been revealed in children with hydrocephalus as well as in premature children (Houliston et al 1999, Hård et al 2004). The structured history taking has been elaborated and revised continuously (Dutton 2003, McCulloch et al 2007).

1.5 EPIDEMIOLOGICAL LONG-TERM FOLLOW-UP STUDIES

In follow-up studies prematurity has preferentially been defined according to BW, as the GA has been more difficult to ascertain. The BW is traditionally categorized into three groups, implying the possibility of comparing results: Low BW (LBW) $\leq$ 2500 g, Very Low Birth Weight (VLBW) $\leq$ 1500 g and Extremely Low BW (ELBW) $\leq$ 1000 g. With the advent of ultrasonography assessment, measurement of fetal skeletal growth and thus age has made it possible to settle the GA more adequately for defining prematurity. However, during 1987-88 when the adolescents in the current study were born, the birth weight was still the dominant measure of prematurity, and still is in many parts of the world. The varied definitions of prematurity make comparisons between different studies somewhat difficult. Furthermore the development of visual and cognitive functions is proceeding during childhood up to adolescence, as described above and hence comparisons between different age groups can be hazardous. Table 1 shows different follow-up studies on visual and cognitive outcome of children born prematurely from 12 years of age and up. Growth deviation at birth, either as abnormally low birth weight or abnormally high birth weight with respect to GA is defined according to distribution of normal population data. Thus a BW less than 2 standard deviations (SD) from mean weight related to GA is defined as small for gestational age (SGA). Both preterm and term infants can be born SGA.

Table 1. Follow-up studies of prematurely born adolescents regarding visual and cognitive outcome

First Author Year of publication	Nation	Age studied (years)	Number of subjects (n)	Study subjects
Fledelius 1981	Denmark	10-18	137	LBW
Rickards 1988	Australia	14	140	VLBW
Powls 1997	UK	11-13	137	VLBW, <31w
Botting 1998	UK	12	138	VLBW
Saigal 2000	Canada	12-16	150	ELBW
Doyle 2000	Texas, USA	14	154	VLBW
Rickards 2001	Australia	14	130	VLBW (CP excluded)
Abernethy 2002	UK	13	87	VLBW
Hack 2002	Ohio, USA	20	242	VLBW
O'Connor 2002, 2006	UK	12	293	<1700g
Taylor 2004	Ohio, USA	14	67/64	ELBW/VLBW
O'Brien 2004	UK	15	151	<33w
Stephenson 2007	UK	11-14	198	<1700g
Hellgren 2007	Sweden	15	59	VLBW
Lindqvist 2007, 2008	Norway	14	51/59	VLBW/SGA
Gäddlin et al 2008a	Sweden	15	61	VLBW
Weisglas-Kuperus 2008	Netherlands	19	596	<32w and/or VLBW

2 AIMS OF THE THESIS

The aims of this thesis were first to describe different aspects of visual and cognitive functions in a population-based group of 15 year old VLBW subjects in comparison with a matched control group. Second, the aims were to investigate associations between functional outcome and brain MRI findings as well as optic disc measurements in the VLBW group.
The aims according to papers were:

Paper I
To describe visual functions and relate them to MRI findings and the intelligence test parameters in adolescents with VLBW.

Paper II
To evaluate visual fields and optic disc morphology in VLBW adolescents compared with age and gender matched controls, and to relate the findings to MRI results.

Paper III
To describe ocular alignment and stereo acuity in adolescents with VLBW in comparison with a matched control group and to investigate associations with WMDI and visuo-spatial skills in the VLBW group.

Paper IV
To describe fixation behavior assessed with an infrared eye tracking device in VLBW adolescents and age matched control subjects and relate the findings to WMDI and to visuo-spatial performance.

3 MATERIAL

This prospective nested case-control study was initiated by a group of pediatricians. Several reports of the cohorts have been published (Bylund et al 1998, Samuelsson et al 1999, Bylund et al 2000, Finnström et al 2003, Mai et al 2003, Samuelsson et al 2006, Gäddlin et al 2007, 2008a, 2008b).

VLBW group

The original study group comprised all live born VLBW infants (n = 107) born in the southeast region of Sweden (the counties of Jönköping, Kalmar and Östergötland with a total population of 935 000) between 1 February 1987 and 30 April 1988. The incidence of VLBW newborns was 0.72%.

Considerable efforts had been made to obtain a complete registration of all newborns. A total of 86 VLBW infants survived the neonatal period and were eligible for a prospective follow-up study.

Antenatal steroids had been given to 18% of the mothers. No surfactant treatment was given at the time. The survival rates were 0/1 in week 24, 2/7 in week 25 and 3/6 in week 26. From week 27 to week 32 the survival rate was about 80% and from week 33 almost 100%.

The VLBW infants were screened for ROP at the age of 40 postmenstrual weeks, according to the clinical practice at the time. Two VLBW subjects had diagnosed ROP stage two or higher. None were treated for ROP. One infant had Down syndrome and was excluded from the follow-up study in the neonatal period.

Two subjects with WMDI were excluded from further follow-up at four years of age because of inability to participate in tests. Of the remaining 83 subjects, 22 did not accept the invitation to participate in the current study, and two had moved abroad. Thus, 59 (69%) VLBW subjects participated in the 15 year follow-up study.

Control group

A control group was selected in the neonatal period. For each VLBW newborn who survived the first two days, an infant born term and next in order to the VLBW infant, with the same gender and parity and without malformation, was included. The control infant was born at the same hospital or at the hospital where the VLBW infant should have been born, if the mother had not been referred. A total of 86 control infants participated from start. Of these 55 (64%) agreed to participate in the current follow-up study. Since the pair-matching was no longer complete, group comparisons were conducted.

Clinical data of the participants are presented in Table 2.

Table 2. Demographic and clinical data of the participants in the follow-up study. Mean (range)

	Controls		VLBW	
N	55		59	
Gender	Female, n = 26	Male, n = 29	Female, n=26	Male, n = 33
Birth weight (g)	3470 (2690-4600)	3621 (2230-4570)	1195 (860-1500)	1199 (685-1495)
SGA	0	1	17	18
GA (weeks)	40 (38-42)	40 (37-42)	32 (27-38)	31 (26-35)
CP	0	0	0	5

GA = gestational age, SGA = small for gestational age, CP = cerebral palsy

Dropouts

The dropouts were born at a mean GA of 30 weeks (range 25–35) and the participants at 31 weeks (range 25–37; p=0.039). Two excluded girls born at GA 26 and 27 weeks had WMDI, diagnosed with MRI and CT. One had shunted hydrocephalus, severe quadriplegia, severe mental retardation and esotropia and the other had moderate diplegia, severe mental retardation, autism and blindness due to ROP. One infant with Down syndrome was born at 28 weeks GA. When these three subjects were excluded from analysis, the difference in GA was no longer significant between the participants and the dropouts. Clinical data of the dropouts including the three excluded subjects are presented in Table 3.

Table 3. Demographic and clinical data of the dropouts, including the 3 excluded subjects. Mean (range)

	Controls		VLBW	
N	31*		27	
Gender	Female, n=15	Male, n=15	Female, n=14	Male, n=13
Birth weight (g)	3644 (2460-4860)	3635 (2830-4430)	1176 (740-1495)	1177 (745-1460)
SGA	0	0	4	5
GA (weeks)	40 (38-42)	40 (37-42)	30 (25-35)	30 (26-32)
CP			2	2

* One missing data, GA = gestational age, SGA = small for gestational age, CP = cerebral palsy

Visual acuity levels including the dropout group

Data from VA assessments at 4 and 12 years and from medical records were collected from 83/86 (97%) of the VLBW subjects and from 82/86 (95%) control subjects (Finnström et al 2003).

In conclusion three (4%) VLBW subjects (the subject with Down syndrome not included) had binocular VA worse than 0.3, i.e. visual impairment as classified according to the World Health Organization 2007. No control subject had visual impairment.

4 METHODS

4.1 STRUCTURE

4.1.1 Magnetic resonance imaging

MRI examinations of the brain were conducted at six local hospitals. The adapted imaging protocols followed a predefined guideline. The imaging sequences included a T1-weighted sagittal, T2-weighted transaxial and coronal, fluid-attenuated inversion recovery (FLAIR) and T1-weighted inversion recovery (IR) coronal acquisitions. The same two pediatric neuroradiologists assessed MR images in consensus. WMDI was defined as increased focal signal intensities in the T2-weighted and FLAIR images, indicating astrogliosis. This is the result of astrocyte reaction to the brain damages induced beyond GA 28 weeks. The WMDI findings were classified as mild (loss of <25% of periventricular white matter or only gliosis), moderate (loss of 25% to 50% of periventricular white matter) or severe abnormality (>50% loss of periventricular white matter).

4.1.2 Ocular fundus

Optic disc
Digital fundus photographs were obtained using cameras at five different settings. Only correctly focused photographs from right eyes with the optic disc centered and the macula well defined were accepted for analysis.
Optic disc parameters were evaluated by marking the endpoints of the long and short diameter of the optic disc and cup, assuming elliptical shape (Williams 1987). The optic rim area was defined by subtraction of the cup area from the disc area. In order to compensate for differences in magnification due to camera and eye optics, the centre of the macula was marked. The macula-disc centre measure is reported to be quite constant among adults (Mok & Lee 2002). This macula-optic disc centre distance was used as reference measure (Wakakura & Alvarez 1987, Williams 1987, Williams & Wilkingson 1992) when converting pixel units to metric distance (Bartling et al 2008). The evaluations were made by two independent observers with practically identical result (r= 0.93). The optic disc cup, optic disc area, optic rim area and the optic rim area/optic disc area were used as outcome measures.

Retinal vasculature
The tortuosity of the retinal arterioles (ITA) and the vascular branching points (BP) were calculated, using digital analysis (Strömland et al 1995). Measurements were made by tracing each vessel (path length) from its origin on the optic disc to a reference circle with a radius of 3.0 mm from the geometric centre of the optic disc. The ITA was calculated from the length index, i.e. the path length of the vessel divided by the linear distance from the vessel origin to the reference circle. Vessels were also traced from their branching point to the reference circle, and the total number of branching points,

i.e. the number of retinal vessels within this area, was calculated. Due to different magnifications in the four cameras used, the analyses of branching points resulted in relative values and not absolute values. All measurements were made without knowledge of identity and diagnosis of the study subjects.

4.1.3 Refraction

Cycloplegic refraction in both eyes was measured using auto refraction 40 minutes after instillation of one drop of a combination of 0.85% cyclopentholate and 1.5% phenylephrine. Myopia was defined as ≥ -0.5 D in any eye (spherical equivalent), hyperopia as ≥ 2 D in any eye (spherical equivalent), and astigmatism as >1 D cylindrical error in any eye (Negrel et al 2000). Anisometropia was defined as a difference in cycloplegic refraction ≥ 1D (spherical equivalent), between the eyes.

4.2 FUNCTION

4.2.1 Visual Function

Visual acuity
Best corrected monocular and binocular distance VA was assessed with the line letter KM chart (Moutakis et al 2004), based on seven letters with similar legibility. The progression is geometric and the maximal measurable VA is 2.0 (decimal). The KM chart is designed for a testing distance of 3 m. Best corrected binocular distance VA was also assessed with single optotypes. VA was defined according to clinical practice as at least 70% correctly read letters and is expressed as decimal (Hedin & Olsson 1984). Best corrected linear VA was assessed at near with a maximal measurable VA of 1.0.
In paper III we defined a better and a worse eye based on VA in each subject, and we used the definition of subnormal VA as either worse than 1.0 binocularly, or monocularly in combination with an interocular VA difference of more than two lines (Ohlsson 2001, O'Connor et al 2004).
A crowding ratio was calculated by dividing binocular VA assessed with single letters with binocular VA assessed with letters in line. Crowding was defined as a crowding ratio ≥ 2 (Pike et al 1994).
In paper IV the better (BE) and the worse eye (WE) was defined according to fixation behavior not always corresponding to the better or worse eye according to VA.

Visual field
The computerized Rarebit Perimetry (RB) was used for evaluation of the VFs. Rarebit perimetry depends on standard personal computer (PC) components. The testing was carried out in a dark room, at two distances; at 50 cm and at 1m. The longer distance was used for the 5-10 degree central visual field. No headrest was necessary since comfortably seated subjects will sit still enough. Examinations were performed with habitual correction on right eyes.

The technique has previously been described in detail and has been shown to be sensitive to damage in the visual pathways of different origin (Frisén 2002, Martin & Wanger 2004, Martin 2005, Brusini et al 2005, Gedik et al 2007). The software is available free of charge at http://www.oft.gu.se/webdiagnos. RB has been found suitable for children (Martin 2005), due to the short examination time and the subsequent short attention time span needed, and it has shown good correlation with optic disc abnormality in pediatric glaucoma patients (Martin & Nilsson 2007).
The principle relies on testing the integrity of the retino-cortical detector matrix with very small bright dots, less than 0.5 MAR (minimum angle of resolution) in the tested area, presented one or two at the time. Dark adaptation is not necessary (Frisén 2002).
The subjects respond by single or double mouse clicks, depending of the number of perceived dots. Ten percent of the presentations contain one or no dot, and are used for control purpose. These numbers of false-positives, expressed as "errors" in the result presentation, are used as a measure of the reliability of the test results. Stimuli are presented in 24 separate test areas within the 30 x 20 degree VF and fixation is encouraged by dynamically changing the location of the fixation mark. Since the retino-cortical detector matrix normally is complete, with no gaps between the receptive fields, a normal person will have a hit rate of nearly 100%. Loss of receptive fields gives a lower hit rate (Frisén 2002). The results are summarized in two measures, the RB mean hit rate (MHR), which is used in the current study, and the number of locations with a hit rate below 90%. In a previous study of healthy subjects aged 14 to 20 years, normal MHR ranged from 89% to 100% with a median of 97% (Martin 2005).

Stereo acuity
Stereo acuity was assessed with the TNO stereo test (1992). Normal stereo acuity was defined as a resolution of 60 sec of arc or less (Powls et al 1997, Hård et al 2000, Lindqvist et al 2008). Subjects with no quantitatively measurable stereo acuity were assigned a nominal high score (1000'').

4.2.2 Oculomotor control

Ocular alignment
The ocular alignment was evaluated with the cover test, for qualitative detection of heterotropia, as well as the horizontal Maddox rod test, for quantitative evaluation of heterophoria (Michaels 1980). Both tests were performed at distance (3 m) and at near (0.33m) with habitual correction and in the case of cover test without it.
Exophoria was defined as values below the 5^{th} percentile in the control group and esophoria as values above the 95^{th} percentile. Thus, the cut off values, defining heterophoria in the present study (exophoria was defined as negative values and esophoria as positive), were at distance exophoria < - 4 prism dioptres (pD) and esophoria > 3pD and at near exophoria < - 8pD and esophoria >4pD. Medical records from the children in both groups were reviewed to identify previous strabismus surgery. Ocular misalignment was defined as the presence of heterotropia or heterophoria.

Visual fixation

During this investigation the subjects wore infrared (IR) goggles (XY-1000, from IOTA Inc, Timrå, Sweden) and the eye position (four channels; right and left eyes, horizontal and vertical) was sampled at 500 Hz. The experiment started with a monocular three-point calibration which was run for 15 seconds. A single blinking fixation dot (subtending a visual angle of 0.4 deg.) was presented in the center of the screen and the subject was asked to keep the fixation as steady as possible on the dot for 30 seconds. The data was calibrated using the JR program (Bolzani et al 1998, Ygge et al 1999) and then the following parameters were analyzed: the number of blinks, the number of drifts larger than 3 degs, the number of saccades with amplitude larger than 5 degs, the fixation distribution, and the vergence eye position. The fixation distribution was used to define the better eye (BE) and the worse eye (WE).

4.2.3 Cognitive function

Intellectual level

We used the Swedish version of the WISC-III (Wechsler 1999), a standardized test to measure children's cognitive skills. WISC-III does not require reading or writing. The scale comprises ten subscales that are organized in two groups: verbal tests (VIQ) and visuo-spatial, performance tests (PIQ), see table 4 and 5. The total score of the two tests can be converted to a full-scale intelligence quotient (FSIQ) score comparable with population-based normative data. The mean FSIQ in a normal population is 100±15 units; a FSIQ below -2 SD (FSIQ < 70) is regarded as having learning disability or mental retardation (Wechsler 1999). PIQ was used as a measure of visuo-spatial skills (Paper III & IV), and PIQ < 70 was regarded as deficient.

Table 4. Verbal subtests

Subtest	**Description**
Information	Oral, "trivia"-style. General information questions
Similarities	Explaining how two different things or concepts could be alike
Arithmetic	Oral, verbally framed math application problems, no visual aid
Vocabulary	Giving oral definitions of words
Comprehension	Oral questions of social and practical understanding

Table 5. Performance subtests

Subtest	**Description**
Picture completion	Identifying missing parts of pictures
Coding	Transcribing a digit-symbol code as quickly as possible
Picture arrangement	Sequencing cartoon pictures to make sensible stories
Block design	Copying small geometric designs with four or nine larger plastic cubes
Object assembly	Puzzles of cut-apart silhouette objects with no outline pieces

Structured history taking

A structured history regarding problems in five areas (face recognition, spatial orientation, perception of depth and motion, and simultaneous perception) was taken to identify and characterize remaining visual difficulties (Table 6).

Table 6. Areas of cognitive visual problems and questions asked

Area of cognitive visual problem	**Problems or difficulties asked for**
Depth perception	Walking in stairs
	Walking on uneven ground
	Estimating distance/depth
Recognition	Recognizing familiar faces in unusual environments
Simultaneous perception	Doing a jigsaw puzzle
	Finding things on a patterned carpet/noisy background
Movement perception	Perceiving a moving object/perceiving an object while moving
Spatial orientation	Finding the way (orientating) with the sense of location

4.3 STATISTICS

For group comparisons, the Mann-Whitney U-test was used in paper I-III, and unpaired t-test with Welch correction in paper II-IV. For comparisons of proportions, the Chi^2 test was used in paper I and the Fisher Exact Test in paper I-IV. For linear regression the ANOVA-test was used in paper I, and the Spearman rank correlation test for correlations in paper II and IV. In paper IV one-way analysis of variance with the Tukey post hoc tests were performed. A p-value <0.05 was considered statistically significant.

Calculations and graphs were performed in SPSS V 13.0 (SPSS Inc.) in all papers, except for paper IV, where the calculations and plottings were carried out in Origin Scientific Graphing and Analysis Software, version 7 (Microcal Inc.).

4.4 ETHICS

The study was approved by The Ethical Committee, Faculty of Health Sciences, Linköping University and performed according to the Helsinki declaration. Written informed consent was obtained from all children and their parents prior to enrolment.

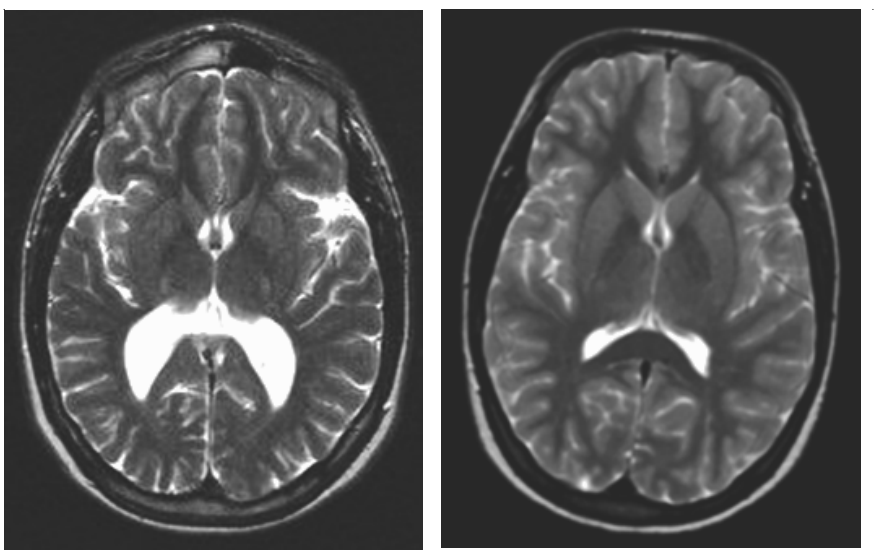
5 RESULTS

5.1 STRUCTURE

5.1.1 Magnetic resonance imaging

Fifty-seven (97%) VLBW subjects underwent MRI. Seventeen subjects had abnormal MRI findings; 16 had WMDI (28%) and one had a malformation. Thirteen were classified as having mild, one as having moderate and two as having severe WMDI. WMDI was located posterior in all subjects. Both subjects with severe WMDI had shunted post hemorrhagic hydrocephalus, one of whom had a discrete hemiplegia and the other a moderate diplegia. The malformation was localized to the cerebellum and also included a neuronal migration disturbance in the left cerebrum. Figure 2 shows T2 weighted transaxial MRI of two VLBW participants.

Figure 2. MRI of VLBW subjects in the study.



Left picture: Moderate posterior WMDI. Note the wide (white) posterior horns of the ventricles and decreased adjacent white matter (black on the picture). **Right picture:** Normal MRI findings

5.1.2 Ocular fundus

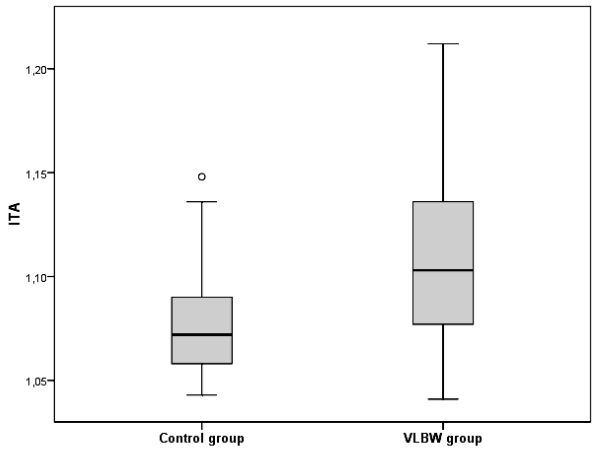
Optic disc

The optic disc area was equal in the studied groups, but the optic cup area was significantly larger ($p = 0.013$) in the VLBW group and, consequently, the optic rim area ($p = 0.018$) and the optic rim/optic disc ratio ($p = 0.012$) were smaller. The difference in mean optic rim area between the VLBW subjects and the control group corresponds to 9% (1.77 ± 0.36 mm^2 and 1.95 ± 0.43 mm^2, respectively). No correlations were found between optic disc parameters and RB results.

Retinal vasculature

There was a significant difference in ITA ($p < 0.001$) between the groups (Figure 3 and Figure 4), but not in the number of vessel branching points ($p = 0.57$).

Figure 3. Arterial tortuosity in the studied groups.



ITA=index of arterial tortuosity, bold lines=medians, boxes=interquartile range, whiskers=1.5 x interquartile range, ring=outlier (< 3 x interquartile range)

No significant difference was found in optic disc variables or arterial tortuosity between VLBW subjects with and without abnormal MRI findings. The three subjects with moderate to severe WMDI had less arterial tortuosity and fewer retinal vessel branching points, and two of them also had smaller rim areas compared with those with mild WMDI.

Figure 4. Ocular fundus of the right eyes in one VLBW (left) and one control (right) subject

VLBW subject with marked arterial tortuosity
ITA = 1.18
Optic disc area=1.7 mm^2
Optic rim area=1.65 mm^2

Control subject with normal arterial tortuosity
ITA= 1.04
Optic disc area=2.43 mm^2
Optic rim area=1.95 mm^2

5.1.3 Refraction

Significantly more VLBW subjects (11/58; 19%) had astigmatic refractive errors than controls (0/55) ($p<0.001$). Fourteen of 58 (24%) VLBW adolescents and 10/55 (18%) control subjects were myopic according to the predefined criteria (n.s.). Hyperopia was found in 9/58 (16%) VLBW subjects and in 5/55 (9%) control subjects (n.s.). There was no significant difference in refraction (spherical equivalent) between the groups in either eye (Table 7). Anisometropia was found in three VLBW subjects and in two control subjects. No association was found between heterophoria and refraction.

Table 7. Cycloplegic refraction in both groups, mean ± SD (range)

	VLBW subjects		**Control subjects**	
	Right eyes	Left eyes	Right eyes	Left eyes
Spherical equivalent	0.5 ± 2.5 (-10.1 – 6.1)	0.6 ± 2.4 (-9.4 – 5.7)	0.5 ± 1.4 (-3.9 – 4.4)	0.5 ± 1.5 (-4.5 – 5.2)
Astigmatism	-0.6 ± 0.8 (-4.25 – 0)	-0.5 ± 0.7 (-3.5 – 0)	-0.4 ± 0.4 (-1 – 0)	-0.2 ± 0.3 (-1 – 0)

Myopia was significantly more common among the VLBW subjects with WMDI than among the subjects with normal MRI findings (7/16 [44%] and 6/40 [15%]; p=0.035). Anisometropia was not more common in the WMDI group.

5.2 FUNCTION

5.2.1 Visual function

Visual acuity

Best corrected VA at 3 m is presented in Table 8. The median value of best corrected binocular near VA was 1.0 (range 0.25 – 1.0) in the VLBW group and 1.0 (0.8 – 1.0) in the control group (n.s.).

Best corrected binocular line VA was significantly lower in VLBW subjects with refractive errors than in emmetropic VLBW subjects (p=0.004). The difference was no longer significant when the subjects with WMDI were excluded from the analysis (p=0.163).

Table 8. Median decimal best corrected VA (range) in both groups

	VLBW	Control	p
Binocular line	1.3 (0.25 – 2.0)	1.6 (0.8 – 2.0)	0.004
Binocular single	1.3 (0.65 – 2.0)	1.6 (1.0 – 2.0)	0.008
Better eye *	1.3 (0.06 – 2.0)	1.6 (0.8 – 2.0)	0.013
Worse eye*	1.3 (0.06 – 1.6)	1.3 (0.2 – 2.0)	0.011

*Better and worse eye refers to VA as defined in paper III

We found no significant difference regarding distance binocular or better eye VA between the VLBW subjects with and without WMDI. The VLBW subjects with WMDI had significantly lower VA in the worse eye (p=0.041).

Two control (4%) and four VLBW subjects (7%) had subnormal VA according to the predefined criteria (Paper III). They all had refractive errors and/or ocular misalignment. Three of the four VLBW subjects had astigmatism and in addition moderate to severe WMDI.

One control subject (who also had refractive esotropia), of the five control and VLBW subjects with anisometropia, had subnormal VA.

Visual field

The results from the control group did not differ significantly from those previously described (Martin 2005). There was no significant difference in RB MHR between the groups, but the difference between the superior and inferior hemifields was larger in the VLBW subjects (p = 0.02). Ten of the 57 VLBW subjects (p = 0.022) had subnormal VF results defined as an MHR below the fifth percentile of the controls (i.e. < 89%), and all of these also had a significantly lower MHR (p = 0.039) in the inferior hemifield compared to the superior. Six of 15 subjects with WMDI (who underwent VF testing) and four of 39 without MRI pathology had subnormal RB VF results (p = 0.020).

Stereo acuity

Thirteen VLBW adolescents (22%) and three controls (5%) had subnormal stereo acuity (p=0.011). The median value of stereo acuity (heterotropia excluded) for the control group was 30´´ (range 15'' – 1000'') and for the VLBW group 60´´ (range 30'' – 1000''; p<0.001).

Esophoria, but not exophoria was associated with subnormal stereo acuity (p=0.027).

Stereo acuity was significantly lower in the 12 VLBW subjects with PIQ < 70 (median 180'', range 30 – 1000'') compared to the 45 with PIQ ≥ 70 (median 60'', range 30 – 240''; p=0.002). There was no significant difference neither when comparing VLBW subjects with corresponding cutoff levels of VIQ (p=0.332) or FSIQ (p=0.182), nor when analyzing the control group in the same way.

The VLBW subjects with subnormal stereo acuity had significantly more cognitive visual problems according to the structured history taking (p=0.011).

Six of the 16 (38%) VLBW subjects with WMDI had subnormal stereo acuity compared to 5/40 (13%) without (p=0.059).

The difference in distance binocular VA (p=0.01), stereo acuity (p=0.01) and prevalence of astigmatism (p=0.004) between the VLBW adolescents and the controls persisted when we compared the VLBW adolescents with normal MRI results (n=40) with the controls (n=55).

5.2.2 Oculomotor control

Ocular alignment

The cover test revealed one control subject with refractive esotropia. Three VLBW subjects had esotropia and one had exotropia and hypotropia. Medical records disclosed two additional VLBW subjects who had previously been surgically treated for intermittent exotropia, in the current study they were diagnosed as having exophoria. One VLBW subject had a bilateral Brown syndrome.

Nine VLBW subjects (16%) had heterophoria at distance (exophoria; n=6, esophoria; n=3) compared to 4% of the control subjects (p=0.026). Five VLBW subjects (9%) had heterophoria at near (exophoria; n=2, esophoria; n=3) compared to one control (p=0.206). Exophoria at near and distance was significantly more common in the VLBW group (15%) than in the control group (0%; p=0.006) but not esophoria (7% and 4% respectively; p=0.679). The two VLBW subjects surgically treated for intermittent exotropia had exophoria, one at distance and the other at near.

Thus thirteen VLBW subjects (22%) had ocular misalignment with habitual correction at distance. Ocular misalignment was significantly more common in the VLBW group with WMDI (44%) and without (15%) than in the control group (4%; p=0.001).

Six of 13 (46%) VLBW subjects with ocular misalignment and 6/44 (14%) without ocular misalignment had PIQ < 70 (p=0.020).

Nystagmus was seen in the three VLBW subjects with moderate to severe WMDI.

Visual fixation

The participating VLBW subjects (n=18) had more horizontal vergence instability than the control subjects (n=29; means 2.4±2.0 and 1.3±0.8 degs respectively; p=0.035).

The VLBW subjects showed a larger distribution of fixation points in the better and the worse eye, than the control group. However the variability was large both within the groups and between the groups and no significant differences were found.

WMDI was found in seven (39%; 6 mild and one severe) of the 18 VLBW subjects. The distribution of fixation points of the WE was significantly larger in the VLBW group with WMDI (3.2±2.1 degs) than in the control group (p=0.016). The VLBW subjects with WMDI had mean vergence instability 3.9±2.4 degs and significantly more than the controls (p=0.001). The significance persisted when comparing the VLBW subjects with mild WMDI with the controls (p=0.003). The VLBW subjects with normal MRI findings had mean vergence instability 1.5±1.0 degs and not significantly more than the control group (p=0.939). The difference in vergence instability was significant when comparing the VLBW subjects with WMDI with those without (p=0.010).

Mean PIQ in the VLBW group with and without WMDI was 78±25 and 93±18 respectively compared to the control group (99±15). The difference between the controls and the VLBW subjects with WMDI was significant (p=0.016). There was a significant negative correlation between PIQ and horizontal vergence instability in the VLBW group (corr coeff 0.509; p=0.031) but not in the control group (p=0.595). There was no significant correlation between VIQ and horizontal vergence instability in the VLBW or the control group (p=0.243 and p=0.380 respectively).

5.2.3 Cognitive function

Intellectual level

Two of the 59 VLBW subjects did not perform the WISC-III test and one failed to complete all 10 subtests. The five subtests he did complete were all severely subnormal (both verbal and performance). Eleven of the VLBW subjects had FSIQ < 70 compared with one in the control group (p=0.002) Eleven VLBW adolescents and three controls had PIQ < 70 (p=0.024), and nine VLBW adolescents had VIQ < 70 versus one control (p=0.016). See Table 9.

Table 9. WISC results in studied groups, mean ± SD

	VLBW	Control	p-value
FSIQ	85 ± 18	97 ± 13	< 0.001
PIQ	87 ± 20	99 ± 16	0.001
VIQ	86 ± 17	97 ± 13	< 0.001

Intellectual level and visual function

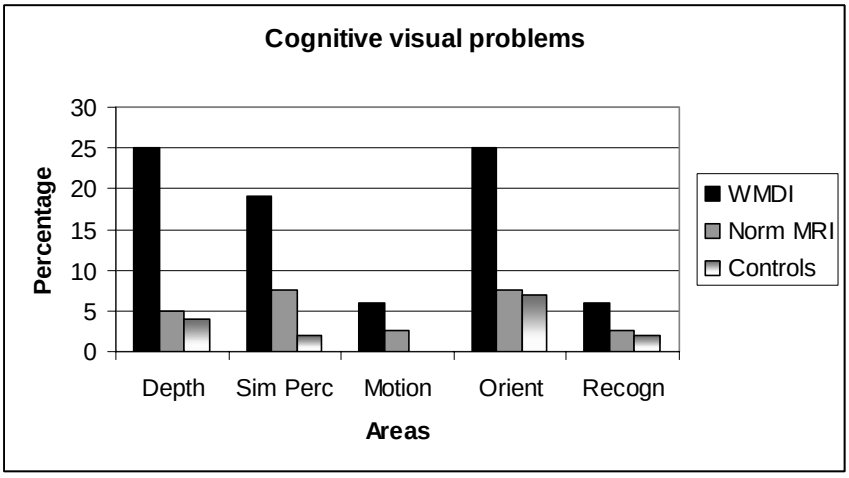
The control group showed no significant association between subnormal WISC results and visual outcome. VLBW adolescents with FSIQ < 70 had significantly lower binocular VA (p<0.001), higher frequency of astigmatism (p=0.019), and more persistent visual problems according to the structured history (p=0.032) than the other

VLBW adolescents. The VLBW subjects with PIQ < 70 had significantly lower binocular VA (p=0.014), lower stereopsis (p=0.002) and more persistent visual problems in the structured history taking (p=0.027) than the VLBW subjects with PIQ >70. They also had more ocular misalignment and more vergence instability, although the latter finding was demonstrated in a subgroup (paper IV). For details see table Uh!

Structured history taking

The VLBW adolescents had more visual problems identified by the structured history taking than the controls (Figure 5; p=0.051). Thirteen VLBW subjects (22%) and five controls (9%) had persistent visual problems in at least one area (p=0.074). The VLBW adolescents with WMDI had significantly more persisting cognitive visual problems than those with normal MRI findings (p=0.043).

Figure 5. Cognitive visual problems according to the structured history in the VLBW group with WMDI, with normal MRI and in control group



Depth=depth perception, Sim perc=simultaneous perception, Motion=perception of motion/movements, Orient=spatial orientation, Recogn=recognition of faces

Table 10 shows the significant associations between WISC results, WMDI and visual outcome.

Table 10. Associations between WISC, MRI findings and visual outcome.
Figures represent p-values of associations

	FSIQ	PIQ	VIQ	WMDI
Best corrected binocular VA at distance	<0.001	0.014	<0.001	n.s.
Visual field	n.s.	n.s.	n.s.	0.020
Stereo acuity	n.s.	0.002	n.s.	n.s.
Myopia	n.s.	n.s.	n.s.	0.035
Hyperopia	n.s.	n.s.	n.s.	n.s.
Astigmatism	0.019	n.s.	n.s.	n.s.
Structured history	0.032	0.027	0.007	0.043
Ocular misalignment	n.s.	0.020	n.s.	0.035
Vergence instability (paper IV)*	n.s.	0.031	n.s.	0.010

*Sub groups, see Material

6 DISCUSSION

The aim of this thesis was to describe various aspects of visual outcome in a representative group of VLBW adolescents. Thus the thesis concerns the outcomes regarding visual function, refraction, ocular alignment, fundus morphology, cognitive skills and MRI findings in 15 year old VLBW subjects and matched control subjects from a geographically defined area in Sweden. The hypothesis was that VLBW induces anatomical sequels and that visual and cognitive subnormal functions may still be apparent in adolescence, and that WMDI is associated with visual and cognitive sub normality.

6.1 STRENGTH & LIMITATIONS

Strengths

The original VLBW and control cohorts were selected with respect to time period of birth and geographical region. Considerable efforts had been made to obtain a complete registration of all infants and the cohorts are thought to be representative of the population in the region. The study design was a nested case control study, which entails a lowered risk of selection bias (Ernster 1994). The examination methods are assumed to give an adequate description of useful vision, since structural, functional, perceptual and oculomotor aspects were considered. Two novel techniques, for perimetry and for computerized analysis of optic disc parameters were used. Both of these have been validated in other studies by our research group (Martin & Wanger 2004, Martin 2005, Martin & Nilsson 2007, Bartling et al 2008).

Limitations

The benefit of the original design may have counterbalanced by the high dropout rate at this follow-up after 15 years. However, dropouts are unavoidable in long term follow-up studies (Fewtrell et al 2008). There was a statistically significant difference in mean GA between the VLBW participants (31 weeks) and the dropouts (30 weeks) which may have caused an underestimate of functional and structural sub normality in the VLBW group (Maalouf et al 1999, Hård et al 2000, Inder et al 2005, Jacobson et al 2008).

Two cases with low GA at birth, known WMDI and severe visual and cognitive impairments had been excluded at four years from further follow-up. The addition of data from these subjects would strengthen the associations between morphological and functional sub normality.

The design of ROP screening with one single examination at postmenstrual age 40 weeks did not allow us to acquire information about the prevalence of spontaneously regressed ROP in this group. Therefore comparative analysises with mild ROP were not performed

In Paper IV the inclusion criterion was examination location. There was a higher frequency of WMDI in this VLBW subgroup (39%) compared to the non-participants (24%) although not at a significant level (p=0.239). There is thus a risk of over

estimation of the difference between the VLBW and the control group in fixation data. The small number of subjects in paper IV weakens the conclusions from the study.

6.2 STRUCTURE

6.2.1 WMDI

The prevalence of WMDI, (28%), is similar to that reported by Olsén and co-workers (32%), using standard MRI as in this study (Olsén et al 1997). Higher rates of WMDI in VLBW adolescents have been reported in other studies, using similar MRI technique (Stewart et al 1999, Skranes et al 2008). Reduced cerebral volume and more subtle brain damage have previously been described in VLBW adolescents examined with quantitative and diffusion MRI techniques (Abernethy et al 2002, Vangberg et al 2006). Diffusion tensor imaging has demonstrated an impaired development of myelination in VLBW infants (Inder et al 2005, Skranes et al 2007).
In the current study such brain damage could not be diagnosed, as quantitative and diffusion techniques were not used. Hence, the group with normal MRI findings may have included adolescents with pathology which could have been diagnosed with quantitative and diffusion MRI techniques. The occurrence of brain damage, not detected by the current MRI method, may explain some of the group differences discussed in section 6.2.2.

6.2.2 Ocular fundus

Optic disc
The VLBW subjects had normal optic disc area, but reduced neural optic rim area compared to the control subjects. The finding is in accordance with a report by Jacobson and co-workers of large optic disc cups in normal sized optic discs and with findings from Brodsky showing pseudo glaucomatous cuppings in subjects born preterm with WMDI (Jacobson et al 1997, Brodsky 2001). As far as we know, the presumed mechanism of optic disc cupping in WMDI in children born preterm concerns a decrease in the neuroretinal rim area, which reflects a decrease in the number of axons in the optic nerve. This has been proposed to be caused by retrograde transsynaptic degeneration across the lateral geniculate nucleus (Brodsky & Glasier 1993). This is secondary to the ischemic brain lesion (i.e. WMDI). The brain lesion is acquired in late pregnancy (the 3rd trimester; Krägeloh-Mann 2004) when the surrounding structures of the optic disc have become more rigid, and an adaptation to the smaller number of ganglion cells in the optic disc is unlikely. Consequently, the reduced nerve tissue may result in a normal-sized optic disc with enlarged cupping (Jacobson et al 1997, Hellström 1999). In the current study this variant of optic nerve hypoplasia was not correlated to WMDI, but to VLBW per se. This might be explained by the MRI technique used in the current study.
An enlarged cup size may represent the result of destruction of nerve fibres secondary to increased intraocular pressure. Normal intraocular pressure in premature born subjects was reported by Spierer et al and recently confirmed by Ng and co-workers

(Spierer et al 1994, Ng et al 2008). Another group examined a sample of preterm children with periventricular leukomalacia who were found to have large cups and WMDI, but in whom the intraocular pressure was normal (Jacobson et al 1997). No relationships between optic disc parameters and VF results were found in the current study, making it unlikely that glaucoma would be the cause of the observed optic nerve appearance.

Retinal vasculature

The VLBW adolescents had a significantly higher ITA compared with the controls. In the neonatal period arterial tortuosity in a preterm child is a sign of severe ROP plus disease. However, increased retinal vessel tortuosity has also been documented in other conditions, such as fetal alcohol syndrome and aortic coarctation (Johns et al 1991, Strömland 2004). These conditions seem unlikely in the study group since there was no history or any other clinical finding of maternal alcohol abuse or aortic coarctation. The increased tortuosity is assumed to be due to perinatal hypoxia - a common finding in premature neonates - as has been previously suggested (Bracher 1982). The current VLBW group was not treated with surfactant, which probably added to the pulmonary insufficiency, resulting in hypoxia. Increased arterial tortuosity was not related to WMDI, which might have been expected, since both phenomena possibly have the same etiology. The three VLBW subjects with moderate to severe WMDI had less arterial tortuosity and fewer vessel branching points than the VLBW subjects with mild or no WMDI. This observation may be interpreted as an effect of a diminished need of vascular supply in neural tissue, reduced due to WMDI.

6.2.3 Refraction

Eleven subjects in the VLBW group (19%) had astigmatism compared to none in the control group. Myopia and hyperopia was not significantly more common, although there was a tendency towards more severe refractive errors in the VLBW group. Previous studies, reporting increased rates of refractive errors in preterms, have been carried out in younger populations, before the onset of adolescence (Gallo & Lennerstrand 1991, McGinnity & Bryars 1992, Darlow et al 1997b, O'Connor et al 2002, Larsson et al 2005). In a recent population-based study of VLBW adolescents no increased frequency of refractive errors was found (Lindqvist et al 2007). The myopisation, frequently seen in term born adolescents might have counter balanced the effect of prematurity on refraction (Villarreal et al 2000). Yet, the altered anterior chamber anatomy and bulb length seem to persist in adulthood (Fledelius 1982, Baker & Tasman 2008). Astigmatism was found in the VLBW subjects with moderate to severe WMDI. However, the VLBW subjects without WMDI also had more astigmatism than the control subjects. This might suggest that the mechanism behind astigmatism is complex and possibly linked to the altered growth related to very low birth weight (Ford et al 2000). There was an association between astigmatism and low FSIQ. One may raise the possibility that refractive measurements can identify not only visual problems in preterm individuals, but also potential cognitive deficits.

6.3 FUNCTION

6.3.1 Visual function

Visual acuity

The VLBW adolescents had significantly lower visual acuity than the controls in accordance with previous reports (Powls et al 1997, O'Connor et al 2004, Larsson et al 2005, Lindqvist et al 2007). However, visual impairment, defined by the World Health Organization (VA < 0.3) was found only in one VLBW subject (2%). Moderate to severe WMDI, i.e. lesions to the posterior visual pathways, was associated with bilateral subnormal visual acuity, and also with amblyogenic factors, such as strabismus and refractive errors. Thus the aetiology for subnormal visual acuity in this group of VLBW subjects probably is of two origins; axonal disruption in the optic radiation due to WMDI and superimposed amblyopia. The significant difference in binocular VA between VLBW subjects with and without refractive errors was related to WMDI. When the subjects with WMDI were excluded from the analysis, the difference was no longer significant. This finding strengthens the hypothesis that WMDI plays a major role in the well documented decrease in VA in preterm populations. We have no information on the frequency of ROP, which precludes any correlation analyses.

Crowding was infrequent in the VLBW group, in agreement with other studies (Hård et al 2000, Larsson et al 2005), but in contrast to the increased frequency of crowding, reported in previous studies in younger populations with WMDI (Pike et al 1994). This observation may indicate that crowding improves with increasing age, since our VLBW group was older.

Visual field

Ten out of 57 (18%) VLBW subjects had subnormal results and the inferior VF was relatively more affected than the superior. More VLBW subjects with WMDI had subnormal VFs compared with those with normal MRI results. The reduced sensitivity in the inferior hemifield may indicate that the superior part of the optic radiations is more affected by WMDI than the inferior parts that sub serve the superior VF and whose course through the temporal lobe seem to make them less vulnerable to damage by periventricular leukomalacia (Edmond & Foroozan 2006). Lindqvist and co-workers (2007), using differential light sense perimetry, and O'Connor and co-workers (2004), using the Damato Campimeter, found no differences in VF results in similar studies on similar subjects. However, as O'Connor and co-workers (2004) commented, they may have missed subtle defects because of low sensitivity of the technique. In contrast, Larsson et al (2004) found significant differences using high-pass resolution perimetry. Martin et al (2004) found VF restrictions using RB perimetry, but not using frequency-doubling technology perimetry, in adolescents born after intrauterine growth restriction. The individuals with subnormal VF results had optic disc changes suggesting reduced neuroretinal tissue. This might indicate that RB is more sensitive in detecting subtle restrictions in VF than some other perimetry techniques. Subnormal VF results were related to WMDI. In previous studies WMDI has been documented as a cause of VF

restrictions (Jacobson et al 1996, 2006). In these studies the inferior part of the VF was more affected than the superior, as in the current study.

Stereo acuity

Twenty-two percent of the VLBW subjects had subnormal stereo acuity and the median stereo acuity in the VLBW group was 60'', which was in accordance with previous studies (Hård et al 2000, O'Connor et al 2002, Holmström et al 2006, Lindqvist et al 2008). Lindqvist defined values > 240'' as poor stereo acuity and found 14% in their 14-year old VLBW group. Our corresponding number was 8%, thus somewhat lower. The difference between the VLBW and the control groups in our study reflected a difference in the level rather than in presence of stereo acuity.

There was an association with MRI findings which was no longer significant when the subject with a malformation was excluded, which might indicate that the stereo vision is an unspecific sign of cerebral damage. Mercuri and co-workers (2004) reported an association between lesions involving the basal ganglia and abnormal stereopsis in children who had suffered from neonatal encephalopathy (Mercuri et al 2004). The authors argued that lesions to the optic radiations or the visual cortex were not always related to subnormal visual function. Lindqvist and co-workers reported significantly more VLBW adolescents with subnormal stereo acuity than age matched controls, but when excluding those with diplegia, i.e. a sign of WMDI, the difference declined (Lindqvist et al 2008). Thus, the available evidence seems to indicate a cerebral cause to subnormal stereo acuity.

In the current study stereo acuity was decreased in the VLBW group irrespective of ocular misalignment. This has also been shown in a previous study of similar study groups (Holmström et al 2006). The association between heterophoria and stereo acuity is varying. Stereo vision is shown to be more negatively affected by small angle esophoria than exophoria (Saladin 1995). In the present study no association was found with heterophoria, presumably because exophoria was a more common finding.

Decreased stereo acuity was associated with low PIQ, but not with low VIQ or FSIQ, in line with the findings of Cooke and co-workers (2004), who documented an association between subnormal stereo acuity in preterm children and low FSIQ and PIQ in contrast to VIQ. Jongmans and co-workers (1996) reported deficient stereo acuity in prematurely born children without overt neurological disability and found abnormal stereopsis significantly associated with poor performance on perceptual-motor tests. Thus stereo acuity may well influence the difficulties that VLBW adolescents have with visuo-spatial tasks, or may be an indicator of cognitive visual problems due to a common neurological insult, i.e. WMDI.

6.3.2 Oculomotor control

Ocular misalignment

Ocular misalignment was more common in the VLBW group than in the control group. All VLBW subjects with heterotropia had PIQ < 70 and three of four had moderate to severe WMDI. Strabismus is a well documented finding of various cerebral abnormalities. Increased prevalence of heterotropia and heterophoria has been documented in adolescents with myelomeningocele, as well as in children with hydrocephalus (Lennerstrand et al 1990, Caines et al 2007, Aring et al 2007a). An

association between strabismus and intracranial abnormalities in 11-year-old ex-preterms has been documented (Kok et al 2007). A high rate of strabismus has also been documented in premature children with neurological deficits, such as cerebral palsy, indicating WMDI (Ghasia et al 2008). In a report of seven patients who presented with esotropia as the only clinical sign, six were born preterm and all had WMDI (Muen et al 2007). Visuo-spatial function was not tested, but clinical history revealed subtle neurological deficits in almost all. In accordance with previous studies we found heterotropia mainly in subjects with moderate to severe WMDI and in addition heterophoria in those with less severe WMDI. Thus there seems to be an association between the severity of WMDI and the likelihood of developing ocular misalignment.

Fixation behaviour

The examined subjects were selected from the larger cohort. Comparisons of clinical and ophthalmologic data indicated that they were representative for the total study group. There are few studies providing quantitative data of visual fixation (Newsham et al 2007). In the current study no significant difference between the VLBW subjects and the controls was seen regarding large saccades in terms of its frequency and association with WMDI. No statistical difference in the distribution frequency of fixation points between the VLBW and control groups was noted, although there was a tendency towards a more scattered distribution in the VLBW group. The horizontal vergence instability in the control group was in accordance with a previous study of healthy subjects (Cornell et al 2003). To our knowledge there is no documentation about horizontal vergence instability in adolescents with VLBW or with WMDI. We found an association between WMDI and horizontal vergence instability, which also was correlated to lower visuo-spatial skills, as measured as PIQ. The vergence instability might also reflect accommodation problems, causing retinal blur, which have been reported in children with cerebral lesions (Caines et al 2007). We have previously shown that the VLBW subjects had more exophoria and more heterotropia than the control subjects and also that there was an association with WMDI. The neurocorrelate to vergence eye movements is not entirely known and it seems reasonable to assume that heterophoria and vergence instability are interrelated (Leigh & Zee 2006). Hence one may speculate that the WMDI causes interruption in parts of the ocular motor pathways related to vergence function causing an instable vergence , thus interfering with the fixation stability.

Low fixation performance on a stationary target has been shown to be related to a lower IQ score in a study on healthy young men (Smyrnis et al 2004). Lesions to the parietal lobe can produce problems with instable fixation of stationary targets and in addition convergence and accommodation problems. Problems with visual perception, such as perception of depth, have also been reported (Lynch et al 1977). Visuo-spatial problems have also been described in children born preterm with occipito-parietal periventricular WMDI and have then been defined as a manifestation of cognitive visual dysfunction (Saidkasimova et al 2007). In the present study we found an association between one aspect of fixation, namely vergence instability, and PIQ. The cohorts were small and conclusions must therefore be drawn with caution.

6.3.3 Cognitive function

Intellectual level & cognitive visual function

Eleven VLBW adolescents (20%) had FSIQ < 70 and they also had more visual problems than those with normal FSIQ, i.e. decreased binocular VA, increased frequency of astigmatism and more problems revealed by the structured history taking. PIQ was associated with these abnormalities, except with astigmatism, but also with subnormal stereo acuity and ocular misalignment. We used PIQ as a measure of visuo-spatial skills, which can be argued, since the WISC tests are designed for IQ testing and therefore also have a cognitive component. VLBW subjects are well known to suffer from cognitive problems and therefore a reduced score may indicate reduced IQ, rather than specific visuo-spatial ability.

In the current study FSIQ, VIQ and PIQ were equally decreased in the VLBW group. Nevertheless we found that PIQ but not VIQ was correlated to several visual deficits. Furthermore Ito and co-workers found a good correlation between PIQ results and visual perception as measured with the Frostig Developmental Test of Visual Perception in children with spastic diplegia (Ito et al 1996).

Subnormal PIQ has been reported in children born preterm (Hård et al 2000). In many cases deficient visuo-spatial skills have been associated with diplegia or other signs of WMDI (Koeda & Takeshita 1992, Pagliano et al 2007). We did not observe any significant association between low PIQ and WMDI. However, the structured history revealed visual cognitive problems significantly associated with both deficient cognitive functions and with WMDI. The most common problems were perception of depth, simultaneous perception and spatial orientation. All these qualities are referred to the dorsal stream projections to the parietal lobe. Braddick and co-workers suggested dorsal stream vulnerability to early neurological impairment, based on published data and clinical findings (Gunn et al 2002, Braddick et al 2003). Van Braeckel and co-workers (2008) found impaired visuo-motor processing in preterm-born children without CP. The authors took the finding as an indication of impaired dorsal stream processes. Saidkasimova and co-workers presented a series of normal sighted children with MRI verified occipito-parietal WMDI, who all had cognitive visual symptoms consistent with dorsal stream dysfunction (Saidkasimova et al 2007). Downie and co-workers, finally, studied 11-year old ELBW children and found marked subnormal results on a task, presumed to test dorsal stream processes. The results were associated with several subtests of PIQ (Downie et al 2003). Since only one item in the structured history delt with aspects, assumed to be related to the ventral stream, these problems may not have been detected in the current study. An association with WMDI and subnormal PIQ has also previously been shown, often in combination with strabismus. Koeda & Takeshita (1992) found that visuo-perceptual impairment correlated well to the extent of the brain lesion in children born preterm with spastic diplegia and WMDI. These results seem to agree with our findings, i.e. an association between WMDI, ocular misalignment and visuo-spatial deficits. In the current study 69% (9/13) of the VLBW subjects with ocular misalignment had WMDI and or subnormal visuo-spatial skills. Hence ocular misalignment may be indicative of visuo-spatial deficits.

Male gender has been described to entail a higher risk for worse neurodevelopmental outcome among low birth weight children (Hintz et al 2006). Although we did not find any statistically significant gender differences in the current study group, adolescents with cerebral palsy, those with the worst visual outcome and those with moderate and severe WMDI were all boys.

7 CONCLUSIONS

This study confirms previous observations that adolescents with VLBW are at a disadvantage regarding visual and cognitive outcome compared with adolescents with normal birth weight. Adolescents with WMDI had more pronounced visual and cognitive dysfunction. The tests used in the study seemed to disclose expected subnormalities in the VLBW cohort. They also revealed associations with cognitive deficits.

- WMDI was found in 28% of the VLBW adolescents.

In comparison with the control adolescents:

- Ocular fundus measurements showed reduced neuroretinal rim area in normal sized optic discs and particularly increased tortuosity of retinal arterioles in the VLBW subjects

- Spherical equivalent refractive errors were not more common, but astigmatism was frequent in the VLBW group

- Although within normal ranges the VLBW subjects had lower visual acuity and lower stereo acuity

- Reduced sensitivity within the 30 degree visual field was common in the VLBW group, especially in the inferior visual field

- The VLBW subjects had more ocular misalignment and more vergence instability

- The VLBW subjects had lower IQ and lower verbal and performance skills measured with WISC. Low PIQ was associated with subnormal visual and stereo acuity, cognitive visual problems, ocular misalignment and vergence instability

- A structured history revealed cognitive visual problems, most pronounced within areas consistent with defects of the dorsal stream

-WMDI was associated with visual field sub normality, refractive errors, ocular misalignment, vergence instability and cognitive visual problems

- All VLBW subjects with moderate to severe WMDI had astigmatism, subnormal visual acuity and heterotropia as well as severe cognitive deficits

8 FUTURE PERSPECTIVES

Given that more very immature infants will survive it will be necessary to provide more detailed knowledge of the effects of immaturity and the potential difficulties these survivors will experience. The majority of VLBW individuals seem to escape from deficits, but the ones who don't must be identified. There is evidence that the sequeles do not decrease with age, but might increase (Hack et al 1995, O'Brien et al 2004). WMDI is now considered to be of enormous public health importance because of the large number of prematurely born survivors (Volpe 2009). This fact has implications on clinical and pedagogical routines. The roles of ophthalmologists will probably have to change. Multidisciplinary team work will be unavoidable.

Clinical applications

New clinical guidelines for follow-up will be needed, in particular within the pediatric ophthalmology field. The cognitive and visual deficits of preterm patients will be a challenge, since they comprise invisible handicaps, which actively have to be looked for. A structured history, designed to reveal cognitive visual problems, should be routinely included in the follow-up of prematurely born children. In addition stereo acuity, measured with for example TNO, fundus photographs with digital analysis, quantitative assessments of ocular alignment, refraction, and visual fields should be included. These assessments should be viewed as methods to define disability patterns and to identify, for example cognitive deficits, commonly found in these individuals. Furthermore pediatric ophthalmologists should work within medical teams to gain access to other medical competence.

There is possibly a need to extend the follow-up into adolescence, considering the increasing demands from the society. To succeed with school achievements, make choices of education and occupation and get permission for a driving license are some challenges for preterms. Deficits in simultaneous perception, decreased visual fields and visuomotor problems may form obstacles to achieve these goals, if not taken care of.

Research fields

Diagnostic tools are constantly developing, in particular within the brain imaging techniques (Hüppi & Inder 2001). The magnetic resonance techniques will add knowledge on application of neuroprotective treatment in the newborn brain.

The conclusions of these findings must be considered and clinical correlations evaluated. This is an ongoing vast research field. MRI is now considered the gold standard for diagnosing WMDI. Diffusion tensor imaging (DTI) can visualize more subtle WMDI than standard MRI, thus morphological and functional comparisons need continuous re-evaluation.

Increased knowledge in all visual cognitive functions, in particular visuomotor disabilities is needed. Clinically applicable tools for catching such difficulties have to be developed

Pedagogical possibilities

Can the rate and extent of visual recovery in the early years of life, which occurs ”naturally” for some patterns of brain injury, be facilitated with directed interventions?

At what ages do interventions promote visual recovery for different patterns of brain injury? Is there a critical period for intervention that may be related to the plasticity of the brain or usual maturational processes? The low vision clinics and the pedagogues need to find tools to train disabled children on an individual base.

Improved definition of nervous system damage, e.g. by advanced imaging combined with more detailed analysis of visual, perceptional and cognitive difficulties may lead to new treatment modalities, e.g. using computer game technology (Westerberg & Klingberg 2007). The school system may have to implement new methods based on the findings of such studies.

9 ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to:

The adolescents and their parents for participating in the time consuming tests and examinations.

Lasse, my love, for putting up with most of my frustrations. **Cilla, Katja, Johannes & Maria,** our children for being so wonderful. You never had the chance to choose, and I thank you for everything. You are constantly inspiring me.

Lene Martin, main supervisor and co-author, for encouragement and wise guidance through this jungle of data. Thank you for all your help, the analyses you performed, pleasant discussions and for being available when I needed.

Lena Jacobson, associate supervisor and co-author, for sharing your knowledge in the cognitive visual impairment field and for the interesting and exciting aspects of the discussions. Your enthusiasm for research work has inspired me a lot.

Jan Ygge, associate supervisor and co-author, for friendly guidance particularly within the oculomotor field. Thank you for your diplomatic and sympathetic attitude and for all valuable discussions and comments.

Orvar Finnström, Ingemar Leijon, PO Gäddlin, the original designers of this long-term follow-up study, who invited us to take part in the 15-years follow-up. Thank you for your generous and friendly collaboration.

Ann Hellström, co-author, for your analyses of ocular fundus photographs and for participating in the planning of the study. Thank you also for your energetic and clear comments.

Ying Han, co-author and responsible for analyses of fixation parameters. Thank you for all your efforts and for sharing your knowledge with me.

Olof Flodmark, Marie Wadsby, Eva Aring, co-authors, for fruitful collaboration and for taking part in the examinations. Thank you for interesting discussions.

Chen Wang, for your help with the MRI pictures.

Christina Helander, Ing-Marie Sandberg, for your kindness and skilful coordination of the examinations. Thank you for being so helpful and available.

Elisabeth Berg, for your help with statistical analyses and discussions on statistic matters.

Gunnar Lennerstrand, for valuable discussions and your competent advice.

Lotta Ljungqvist, Anita Rodenkirchen, Nina Hagwall, Gudrun Gunnarsson, for collaboration, friendly acquaintances and help with examinations. Thank you for all your help.

Gerd Holmström and the pediatric ophthalmology team in Uppsala, for flexibility and understanding. Thank you for the years of interesting work together and for showing interest in the study.

Olav Mäepea, for your generous help with SPSS.

Collegues at the Bernadotte Research Lab, for creating such a friendly atmosphere and for your support.

Ulla-Britt Schützler-Peterson, for all your help in practical matters.

The pediatric ophthalmology team at the Ophthalmology section, Astrid Lindgrens Children's Hospital, for a pleasant work atmosphere. Thank you for showing interest in and giving me time for the study.

Kerstin Dahlström, collegues and staff at the Neuropediatric Department, Astrid Lindgrens Children's Hospital, for being so welcoming and supportive.

Eva Åström, for your help and guidance through the thesis template.

Peter Wanger, for your help with analyses. Thank you for joyful discussions and for your enthusiasm mixed with sound scepticism.

Friends in Göteborg and in Sigtuna for your continuous support and reminders of other values than work. Thank you for joy and laughter and pleasant talk.

These studies were financially supported by:
Sigvard & Marianne Bernadotte Research Foundation for Children Eye Care, St. Erik's Eye Research Foundation, Crown Princess Margareta Foundation (KMA), Samariten Foundation, Mayflower Foundation, Solstickan Foundation, Karin Sandqvist Foundation, FORSS – the Medical Research Council of Southeast Sweden

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