VISUAL IMPAIRMENT IN FINNISH CHILDREN

Prevalence, causes and morbidity of full-term and preterm children with visual impairment born from 1972 through 1989

SIRKKA-LIISA RUDANKO

ACADEMIC DISSERTATION

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To Seppo, Leena, and Harri
# ABBREVIATIONS

<table>
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<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>AAV</td>
<td>adeno-associated virus</td>
</tr>
<tr>
<td>BCVA</td>
<td>best corrected visual acuity</td>
</tr>
<tr>
<td>bFGF</td>
<td>basic fibroblast growth factor</td>
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<tr>
<td>BPD</td>
<td>bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>BW</td>
<td>birth weight</td>
</tr>
<tr>
<td>CLN5</td>
<td>variant late infantile neuronal ceroid lipofuscinosis (Finnish type)</td>
</tr>
<tr>
<td>CMV</td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CP</td>
<td>cerebral palsy</td>
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<tr>
<td>CVI</td>
<td>cerebral visual impairment</td>
</tr>
<tr>
<td>DWI</td>
<td>diffusion-weighted imaging</td>
</tr>
<tr>
<td>ELBW</td>
<td>extremely low birth weight (&lt;1000g)</td>
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<tr>
<td>ERG</td>
<td>electroretinography</td>
</tr>
<tr>
<td>FAE</td>
<td>fetal alcohol effect</td>
</tr>
<tr>
<td>FAS</td>
<td>fetal alcohol syndrome</td>
</tr>
<tr>
<td>GA</td>
<td>gestational age</td>
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<tr>
<td>GW</td>
<td>gestational week</td>
</tr>
<tr>
<td>HSV</td>
<td>herpes simplex virus</td>
</tr>
<tr>
<td>IAPB</td>
<td>International Association for the Prevention of Blindness</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>ICH</td>
<td>intracerebral hemorrhage</td>
</tr>
<tr>
<td>ICIDH</td>
<td>International Classification of Impairments, Disabilities, and Handicaps</td>
</tr>
<tr>
<td>INCL</td>
<td>infantile neuronal ceroid lipofuscinosis</td>
</tr>
<tr>
<td>IOL</td>
<td>intraocular lens</td>
</tr>
<tr>
<td>IVH</td>
<td>intraventricular hemorrhage</td>
</tr>
<tr>
<td>LBW</td>
<td>low birth weight (&lt;2500g)</td>
</tr>
<tr>
<td>LCA</td>
<td>Leber’s congenital amaurosis</td>
</tr>
<tr>
<td>LED</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NBW</td>
<td>normal birth weight (≥2500g)</td>
</tr>
<tr>
<td>NCL</td>
<td>neuronal ceroid lipofuscinosis</td>
</tr>
<tr>
<td>ONA</td>
<td>optic nerve atrophy</td>
</tr>
<tr>
<td>ONH</td>
<td>optic nerve hypoplasia</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
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<tr>
<td>PVL</td>
<td>periventricular leucomalacia</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>RDS</td>
<td>respiratory distress syndrome</td>
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<tr>
<td>RLF</td>
<td>retrolental fibroplasia</td>
</tr>
<tr>
<td>ROP</td>
<td>retinopathy of prematurity</td>
</tr>
<tr>
<td>Stakes</td>
<td>National Research and Development Centre for Welfare and Health</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound, ultrasonography</td>
</tr>
<tr>
<td>VA</td>
<td>visual acuity</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>VI</td>
<td>visual impairment</td>
</tr>
<tr>
<td>VLBW</td>
<td>very low birth weight (&lt;1500g)</td>
</tr>
<tr>
<td>vs.</td>
<td>versus</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>XLRS</td>
<td>x-linked retinoschisis, x-linked juvenile retinoschisis</td>
</tr>
</tbody>
</table>
This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-VI).


ABSTRACT

We investigated the prevalence and the causes of childhood visual impairment occurring during the 1970s and 1980s in Finland, with special attention to risk factors and further prevention of visual impairment in children.

The primary data on children with visual impairment were obtained from the Finnish Register of Visual Impairment, one of the patient registers kept up by the National Research and Development Centre for Welfare and Health (Stakes) in Finland and maintained at the Finnish Federation of the Visually Impaired. The data were supplemented from other registers in Stakes and from patient records of the children in Finnish central hospitals.

Visual impairment had been registered, by the 1st of January 1990, in 556 children from a population of 1,138,326 children between ages 0–17, born from 1972 through 1989 in Finland. The age-specific prevalence of visual impairment in children was 49/100,000 in total. Of them, 23/100,000 were blind children and 11/100,000 were children born prematurely.

The main ophthalmic groups of visual impairment were retinal diseases (35%), ocular malformations (29%), and neuro-ophthalmological disorders (29%). Optic nerve atrophy was more common than the other diagnoses of visual impairment (22%), followed by congenital cataract (11%), retinopathy of prematurity (10%), and cerebral visual impairment (8%).

Genetic factors (42%) were the most common etiologies of visual impairment in children, followed by prenatal (30%) and perinatal (21%) factors. Perinatal etiology was most common in preterm children (79%), while genetic and prenatal etiologies were frequent in full-term children (53% and 34%). Neuronal ceroid lipofuscinosis, x-linked juvenile retinoschisis, Leber’s congenital amaurosis, and congenital cataract were the most common inherited causes of visual impairment, present in 45%.

Half of the children were functionally blind (47%). Congenital malformations (52%), systemic diseases (48%), and additional impairments (50%) were common. Boys were impaired more often and more severely than girls. The highest rates of blindness were seen in cerebral visual impairment (83%), retinopathy of prematurity (82%), and Leber’s congenital amaurosis (79%).
In preterm children, retinopathy of prematurity was the predominant ophthalmic disease (46%), followed by optic nerve atrophy (28%) and cerebral visual impairment (12%). Retinopathy of prematurity had developed in the children born at a gestational age of 32 weeks or earlier. It was present in 100% of the visually impaired children with a gestational age of less than 25 weeks or with a birth weight of less than 1000g.

The prevalence of visual impairment in children did not change during the study period of 18 years. The Finnish disease heritage, associated with the geographical isolation of the Finnish population for centuries, influenced the high prevalence of genetic visual impairment in children. Therefore, gene therapies and other new treatments for hereditary eye diseases are urgently needed. The prevalence of congenital malformations and the proportion of prenatal unspecified etiologies were also notably high, presenting great challenges to the Finnish health care.

Significant risks for visual impairment in the 1970s and the 1980s were preterm births, severe perinatal complications, and some serious prenatal disorders, like maternal infections. The incidence of visual impairment was 7 times higher in preterm children than in full-term children. Despite the introduction of systematic eye screening programs for very preterm infants and effective retinal cryo- and laser therapies for retinopathy of prematurity in the 1980s, a rise in blind children was discovered, associating with increases in the survival of very immature preterm infants.

*Keywords:* additional impairment, blindness, cerebral visual impairment, children, congenital cataract, congenital malformation, full-term infant, multiple handicap, optic nerve atrophy, preterm infant, retinopathy of prematurity, visual impairment
ACKNOWLEDGEMENTS

The present study was carried out by the author during 1988 to 2007 in the Finnish Register of Visual Impairment, one of the statistical registers of the National Research and Development Centre for Welfare and Health (Stakes), maintained technically at the Finnish Federation of the Visually Impaired. I am highly indebted to the administrative head of the Finnish Federation of the Visually Impaired, Pentti Lappalainen (MSc) and his successor Mauno Lehtinen (MPolSc) for providing me excellent working facilities and for their interest in my research.

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Helsinki, July 2007

Sirkka-Liisa Rudanko
INTRODUCTION

The prevalence and causes of visual impairment in children depends on geographic regions, socioeconomic development, the status of primary health care, and the eye care services available (Gilbert & Foster 2001). In low-income countries, corneal scars due to measles, ophthalmia neonatorum and other infections, vitamin A deficiency, and harmful traditional eye remedies are major causes for childhood blindness. The prevention of blindness in children has been selected by the World Health Organization (WHO) as an important priority within the VISION 2020 program.

Childhood visual impairment also causes significant medical, educational and social problems for the societies in western countries. Numerous Nordic studies on the subject have been published during the 1900s (Skydsgaard 1955; Vannas & Raivio 1964; Lindstedt 1972; Warburg 1975; Hansen et al 1987; Rosenberg 1987; Fledelius 1990; Blohmé & Tornqvist 1997a). Surveys encompassing the Finnish child population have not, however, been available until the Finnish Register of Visual Impairment was established in 1983. Since 1989, the registration of visually impaired persons in Finland has been obligatory by law, and ophthalmologists have started to register their patients with visual impairment.

During the first half of the 1900s, common causes leading to visual impairment in children were poor hygiene, serious infections, malnutrition with vitamin A deficiency, and unoperated cataract. The causes of visual impairment have changed crucially during the latter half of the 1900s in western countries (Norrie 1967; Lindstedt 1972; Schappert-Kimmijser et al 1975; Forster 1988; Hussain et al 1999; Huo et al 1999; Good et al 2001).

The incidence of the children with combined visual and neurological impairment has increased in western countries during the last two-three decades (Warburg 1975; Rosenberg et al 1996; Olsen et al 1997; Nielsen et al 2007). Unfortunately, the rates of prematurely born children with visual impairment have not decreased, despite new innovations within perinatal care in the beginning of the 1990s.

Further approaches have been sought for the identification of pregnant women with risks of prenatal disorders, preterm delivery, and/or serious perinatal complications (Gencay et al 2001; Hagberg et al 2002; Baker et al 2004; Kataoka et al 2006). The number of the Finnish women using the services of antenatal and infantile-juvenile health care centers has continuously increased. Family counseling has also been arranged for
pregnant women and their spouses, concerning risks for serious hereditary and vision-threatening disorders.

A collaboration of the Nordic registers of visual impairment was initiated by Ruth Riise (Norway) and Mette Warburg (Denmark) in 1988. The project was carried out by a Nordic study group of ophthalmologists, i.e. Mette Warburg and Thomas Rosenberg from Denmark, Gudmundur Viggosson from Iceland, Ruth Riise, Egill Hansen, and Tor Flage from Norway, and Sirkka-Liisa Rudanko from Finland. Consequently, a database on Nordic visual impairment in children was created for research purposes. The need for further investigations on the Finnish material became evident during the Nordic project.

Our aim was to perform the first national cross-sectional study on visual impairment in Finnish children, with special attention to the prevalence, profile, etiologies, and risk factors of visual impairment. Our hypothesis is that preventive measures for visual impairment can be advanced in Finland.
Causes of childhood visual impairment and blindness vary from one part of the world to another (Foster & Gilbert 1992). Childhood blindness is still a major problem in developing countries, where over 80% of the blinding diseases were principally preventable or curable. The four main causes of blindness there are cataract, trachoma, onchocerciasis, and xerophthalmia, followed by measles, congenital rubella, prematurity, and inherited syndromes.

Simple hygienic measures, dietary education, and vitamin A distribution would eradicate a large proportion of visual problems. Antiseptics and antibiotics for the prevention of ophthalmia neonatorum and immunization programs for measles and rubella would also be most desirable. Training for the primary health care workers would reduce harmful traditional practices leading to corneal damage. Attention needs to be paid to the structures of the health care services, surgical techniques, health education, screening to promote early referrals, adequate follow-up, and the training of multidisciplinary teams for specialized pediatric ophthalmological centers. Low vision services are also needed for children in developing countries, e.g. in Latin America, Asia, and Africa.

The possibilities for the blindness prevention and the sight restoration have greatly improved during the last two decades (Thylefors 1998). Still in 1990, however, the number of blind children worldwide was approximately 1.5 million, and 90% of the blind children were living in developing countries. The estimated causes of blindness were retinal diseases (25%), corneal pathology (20%), cataract (13%), glaucoma (6%), and ocular anomalies (17%) (Gilbert & Foster 2001b; Bowman 2005). Modern preventive and therapeutic interventions are efficient for more than 40% of those blinding conditions. The disappearance of xerophthalmia from western countries through dietary improvements by the 1950s is an excellent example of a successful preventive measure.

According to a study carried out in India, the major causes of vision loss in Indian children are cataract (33%), corneal pathology (24%), high refractive errors (12%), glaucoma (11%), retinal diseases (10%), ocular anomalies (8%), and lesions in the higher visual pathways (3%) (Bagchi & Bhattacharya 2006). Unoperated mature cataracts are still seen in around 10% of the children in blind schools in developing countries (Foster & Gilbert 1992).

The program “VISION 2020 – right to sight” was initiated in 1999 by WHO and the International Agency for the Prevention of Blindness, in
order to eliminate all unnecessary global blindness by 2020 (Gilbert & Foster 2001b). The aim is e.g. to reduce the number of blind children to a global average of 40/100,000, i.e. to a half of the current number.

The eradication of chlamydia trachomatis infections in developing countries has been most difficult, despite the SAFE strategy (surgery for trichiasis, antibiotic therapy, facial cleanliness, environmental improvement) organized by WHO for eliminating blinding trachoma globally by the year 2020 (Atik et al 2006; Emerson et al 2006). Mass treatments for all individuals have been given in some African and Asian countries (e.g. Tanzania, Vietnam) and some reduction in the prevalence of trachoma has occurred. Re-emergences after one year from the treatment, however, have been noticed in hyperendemic communities.

In the beginning of the 1900s, serious ocular infections and ophthalmia neonatorum were also prevailing causes of childhood blindness in western countries. The Credé prophylaxis of ophthalmia neonatorum was introduced by Carl Credé, a German gynecologist and obstetrician in the 1800s. Ocular silver nitrate instillation was used to prevent severe congenital infections leading to corneal damage in newborns.

The Credé prophylaxis of ophthalmia neonatorum is still used in many western countries for neonatal vision-threatening infections, especially for chlamydia trachomatis and gonococci (Assadian et al 2002). Instead of 1% silver nitrate, several topical antibiotics and antiseptics are also used for the prophylaxis, e.g. erythromycin, gentamycin, and 2.5% povidone-iodine (Zar 2005). Salvarsan, introduced in 1906 for keratitis due to congenital syphilis, was useful at the time in the prevention of blinding keratitis (Skydsgaard 1955).

Despite extensive social, technological, economical, and cultural developments in the western countries during the latter half of the 1900s, the prevalence of visual impairment in children has not greatly diminished during the last decades. Inherited and neuro-ophthalmological disorders have become more and more prevalent as causes of visual impairment. With increases in preterm births and the survival of extremely low birth weight infants, the rates of blindness and morbidity also seem to increase in children (Tommiska 2001).

### Prevalence of visual impairment in children

The prevalences of childhood visual impairment and blindness between the wealthy and underprivileged societies differ significantly. Despite the data from the developing countries are being only estimates. Detailed comparative data on the prevalence of visual impairment have also been difficult to find in western countries, because the criteria and classifications used by the national registers of visual impairment are seldom uniform.
The data from Canada, the Nordic countries, and the United Kingdom have so far been the most comparable.

In British Columbia in Canada, congenital ocular blindness (visual acuity 0.05 or lower) in children born in 1945–1984 decreased from 80/100,000 live births in the 1940s to 30/100,000 live births in the 1980s (Robinson et al 1987). The rate of congenital rubella infections also decreased, but the incidence of optic nerve lesions increased in 1970–1984.

In Sweden, the prevalence of childhood visual impairment in school children (ages 7–21) was investigated in Uppsala in the 1970s with the help of school consultants for partially sighted school children (Lindstedt 1975). A prevalence of around 70/100,000 children was found, 79/100,000 in boys and 61/100,000 in girls. The etiologies of visual impairment were genetic in 30% of the cases and prenatal or perinatal in 15%. Of prenatal causes 40% remained unspecified. In 1994, the prevalence of visual impairment in Swedish children (ages 0–19) was 109/100,000 according to the newly started registration of children with visual impairment in Sweden (Blohmé & Tornqvist 1997a; Blohmé & Tornqvist 1997b).

In France, the prevalence of children with visual impairment (<9 years) from 1976 through 1985 was 80/100,000 and that of blind children 28/100,000 (Arnaud et al 1998). In Northern Ireland in 1976, the prevalence of visual impairment was 81/100,000, and the proportion of genetic causes was surprisingly high (51%) (Bryars & Archer 1977).

In England in 1981, the prevalence of blindness was 10/100,000 children (0–4 years), 22/100,000 (5–9 years), and 23/100,000 (10–14 years) (Foster & Gilbert 1992).

A standardized form, developed by the International Center for Eye Health and the Program for the Prevention of Blindness (WHO), has been used in London for reporting pediatric visual loss since 1993 (Steinkuller et al 1999). According to some English reports, the prevalence of blindness in children (0–15 years) has been 10–60/100,000 in wealthy western countries (Gilbert et al 1999; Gilbert & Foster 2001b; Rahi et al 2003).

Somewhat higher prevalences of visual impairment in children have also been published in western countries, e.g. 181/100,000 in the United Kingdom by Rogers (1996) and 161/100,000 in Ireland by Flanagan et al (2003).

In Finland in 2005, according to the data of the Finnish Register of Visual Impairment, the prevalence of children with visual impairment (<18 years) is around 70/100,000 and the annual incidence 6/100,000 (Ojamo 2006).

**WHO categories of children with visual impairment**

The severity of visual impairment is commonly classified along the five categories recommended by the World Health Organization and determined by visual acuity (VA) and visual field diameter (Table 2, Appendix).

Some visual disorders are common causes of blindness, e.g. retinopathy...
of prematurity (ROP), neuronal ceroid lipofuscinosis (NCL), and Leber’s congenital amaurosis (LCA). Blindness is often associated with very premature births and with cognitive impairment (Warburg 1975; Nielsen et al 2007). In Sweden in the 1970s–1980s, 26% of the children with visual impairment were classified as functionally blind or totally blind (Blohmé & Tornqvist 1997c).

Gender distribution of children with visual impairment

Visual impairment is more common in boys than girls, but the exact causes of the male dominance are still unknown. The higher disability in boys was already noted in the 1800s, e.g. in the Danish register of visual impairment (Norrie 1927). Disorders with the x-chromosomal transmission of inheritance, optic nerve atrophy caused by perinatal complications, congenital cataract and congenital glaucoma have been more common in male children.

The male preponderance has appeared in most etiological groups (Rosenberg et al 1996; Blohmé & Tornqvist 1997a; Blohmé & Tornqvist 1997c). Higher rates of low 5-minute Apgar score and preterm birth in male children are also seen in the Finnish Perinatal Statistics of the National Research and Development Centre for Welfare and Health (Stakes) (Gissler et al 1996).

The x-linked inheritance can not totally explain the male preponderance in children with visual impairment. Genetic factors may have a more extensive role than previously thought, also in the higher susceptibility to perinatal difficulties among boys.

Diagnoses of visual impairment in children

In the beginning of the 1900s, childhood visual impairment and blindness were mainly caused by congenital malformations and bulbar disorders, xerophthalmia, severe infections, corneal destruction (e.g. due to ophthalmia neonatorum, tuberculosis, syphilis, head lice), by optic nerve atrophy, and retinitis pigmentosa (Norrie 1927).

In the latter half of the 1900s, injuries to the optic nerve and other visual pathways as well as retinal diseases have clearly been increasing in western countries, while the prevalence of infections, e.g. rubella syndrome, has declined due to the extensive immunization program for girls (Robinson et al 1987). Since the 1970s, the most common single diagnoses of visual impairment have been non-hereditary optic nerve atrophy (ONA), cerebral visual impairment (CVI), and retinopathy of prematurity (ROP) (Rosenberg 1987; Häussler et al 1996; Blohmé & Tornqvist 1997b; Blohmé & Tornqvist 1997c; Arnaud et al 1998; Flanagan et al 2003; Rahi et al 2003).
The incidence of brain disorders was 45% in a Nordic incidence study on visual impairment in children in 1993 (Rosenberg et al 1996). The ROP rate increased in the 1980s due to the higher survival of very preterm children along with improvements in the neonatal care, but visual impairment due to ROP has been diminishing again since the 1990s.

**Optic nerve atrophy**

Optic nerve atrophy (ONA) is the most common cause of low vision and blindness in western children, often associated with preterm birth, systemic diseases, and multiple handicap (Robinson et al 1987; Rosenberg et al 1996; O’Keefe et al 2001; Denne et al 2003). Along with the lower perinatal mortality of very preterm infants the incidence of primary and secondary ONA has increased during the last 15 years. A portion of ONA is genetically transmitted. In a part of the cases, the etiology remains unspecific.

**Inherited retinal dystrophies**

Inherited retinal diseases are common causes of childhood visual impairment in developed countries (Gilbert & Foster 2001; Weleber 2002). In Finland, some rare visual diseases have been enriched because of the geographical isolation for centuries.

Genetic diseases have been investigated very intensively for more than 30 years in Finland. The Finnish disease heritage is a group of rare hereditary diseases, mainly monogenic ones, which are overrepresented in Finland due to founder mutations (Varilo et al 1996; Santavuori et al 2000; Sipilä & Aula 2002; Norio 2003).

**Neuronal ceroid lipofuscinoses**

Neuronal ceroid lipofuscinoses (NCL, Batten’s disease) are a group of recessively inherited neurodegenerative lipidoses, prevalent worldwide but enriched in some countries. Four main types of NCL have been recognized, i.e. infantile (INCL, early-onset Batten’s disease), late infantile (Jansky-Bielschowsky), juvenile (Spielmeyer-Vogt-Sjögren, late-onset Batten’s disease), and adult. The childhood forms of the disorder are the most common progressive neurodegenerative diseases in western children (Santavuori 1988; Mole 2004).

According to a Nordic study by Uvebrant and Hagberg (1997), the prevalences of juvenile NCL in 1976–1985 were 1.20/100,000 in Finland, 1.10/100,000 in Iceland, 0.65/100,000 in Norway, 0.46/100,000 in Sweden, and 0.31/100,000 in Denmark. The Nordic incidences of juvenile NCL per 100,000 live births were 7.0 in Iceland, 4.8 in Finland, 3.7 in Norway, 2.2 in Sweden, and 2.0 in Denmark. Juvenile NCL was clearly the most common type of NCL in the Nordic countries. The prevalences of all types of NCL were higher in Finland than in Denmark, Norway, or Sweden.
At least nine clinical NCL gene variants (CLN1–CLN9) are known, and at least six of them (CLN1, CLN2, CLN3, CNL5, CNL6, CNL8) have been genetically identified (Persaud-Sawin et al 2007). The NCL Mutation Database in the United Kingdom (http://www.uc.ac.uk/ncl) contains over 150 NCL gene mutations (Mole 2004). All variant types of NCL cause vision impairment due to retinal dystrophy, mental retardation, motor disturbances, epilepsy and behavioral changes, and lead to early death (Isosomppi et al 2002).

Over 400 patients have been diagnosed in Finland during the last 40 years (Santavuori et al 2000). The ancestors of juvenile NCL (i.e. Spielmeyer-Vogt-Sjögren disease) originate from the southwestern coast of Finland (Mitchison et al 1995). The Finnish variant of late infantile NCL (CLN5) is especially enriched in the western part of Finland (Varilo et al 1996; Goebel 1996). This variant is supposed to be caused by a single founder mutation from the 1500s.

Eye symptoms are usually the first evidence of the disease and the progression of retinal dystrophy is rapid. In cases with juvenile NCL, vision will commonly be affected at the age of 6–7. Typical fundal signs are tapetoretinal degeneration with optic atrophy, narrowed blood vessels, and bull’s-eye maculopathy. Blindness results within one to three years after the onset of visual symptoms. Neurodegeneration leads to progressive motor and intellectual deficits and most patients die before the age of 30 years.

Early diagnosis is mandatory for the prevention of further cases in the families with this severe neurodegenerative disorder. The deposition of abnormal metabolic products in neurons and other tissues, including peripheral blood lymphocytes, allows a reliable specific diagnosis of types, subtypes, and variants of NCL with a minimally invasive test (Rapola & Lake 2005; Anderson et al 2006). The combination of ophthalmological deficits, intracellular inclusions in the conjunctival biopsy, and vacuolated lymphocytes in the peripheral blood is highly characteristic of NCL (Seeliger et al 1997; Santavuori et al 2001). Rapid prenatal or carrier diagnoses by combined genetic and electron microscopic examinations are also possible for infantile, late-infantile, and juvenile types of NCL (Goebel 1996; Rapola et al 1999).

**X-linked juvenile retinoschisis**

X-linked juvenile retinoschisis (XLRS) is probably prevalent throughout the world (The retinoschisis consortium 1998). It is known to be relatively common in Canada, the Netherlands, and the United States. In Finland it is probably more common than in any other country. Visual impairment due to XLRS is clearly more common in Finland than in the other Nordic countries (Forsius 1990; Rudanko et al 1993). XLRS was first described in 1898 by Haas. It is a congenital disorder of retinal development, which leads to cleavages in the sensory retina at
the nerve fiber layer and consequent central and peripheral superficial retinoschisis formations. Radial cystic macular degeneration and peripheral superficial retinal detachments are the main clinical signs. Vitreous hemorrhages occur in around 4% of the cases and retinal detachments develop in around 11% of the cases (Kellner et al 1990). Vitreous hemorrhages usually resolve spontaneously and retinal detachments are treated with conventional buckling procedures. Prophylactic laser coagulation of peripheral retinoschisis is not usually indicated.

The prevalence of XLRS is 1/15,000 to 1/30,000 in Finland. XLRS belongs to the Finnish disease heritage. The relatively high prevalence of XLRS in Finland associates with founder effects, possibly from settlements by two German immigrants in Finland in the 1600s. One family may have spread in the Pori area and one in Kajaani-Oulu area (Vainio–Mattila 1969). Approximately 70% of the cases diagnosed in Finland have originated from western Finland (Huopaniemi et al 1999).

The epidemiology, clinical picture, and molecular genetics of Finnish XLRS families have been extensively investigated in Finland (Forsius et al 1962; Alitalo et al 1988; Forsius et al 1990). The disease gene has been identified, as well as recurrent mutations from small intra-genic deletions to frame shifting insertions, deletions, and splice site mutations. Genetic linkage techniques may be used for diagnosing atypical clinical cases, for prenatal diagnoses, and for carrier detections.

XLRS is the most frequent cause of juvenile macular degeneration in Finnish males. Some homozygous females have also been described. Female carriers have no visual symptoms. Enormous mutation heterogeneity and considerable intrafamilial variations in the age of the onset and progression rate exist. Slow progressive macular changes may lead to seriously reduced central vision after the age of 40. The visual levels vary individually and by age from subnormal vision to profound impairment, and even to nearly total blindness. In the most registered cases, visual impairment is moderate (WHO category 1) and blindness is rare (Vainio–Mattila et al 1969; Forsius et al 1973; Ojamo 2006).

**Leber's congenital amaurosis**

Leber's congenital amaurosis (LCA) is a congenitally inherited retinal dystrophy in children. It is the most common cause of inherited childhood blindness, accounting for 10%–18% of all congenital blindness in western countries (Graw 2003). The incidence is around 2–3/100,000 births. Leber's amaurosis is generally a single retinal disorder without afflictions of other ocular tissues or other organs. Severe malformations and syndromes may, however, be associated, e.g. hydrocephalus, cerebral hypoplasia with motor and cognitive impairment, delayed speech development, cystic kidneys, skeletal anomalies, liver diseases, and other metabolic disorders (Yano et al 1998; Fazzi et al 2003).

LCA can often be suspected soon after birth, but differential diagnostic
problems exist (Grieshaber & Niemeyer 1998). First signs are abnormal visual development, nystagmus and photophobia. The mode of inheritance is generally autosomal recessive. Tens of gene defects and novel mutations cause this disorder (Keen et al 2003). Some mutations seem to also cause other retinal dystrophies, e.g. retinitis pigmentosa and cone-rod dystrophy.

Single mutations of LCA genes cause different clinical pictures, e.g. differences in the origin of symptoms, the progression rate, and the severity of vision impairment, but the disease often has an early onset with very severe retinal degeneration and near-total blindness (Sitorus et al 2003). The ophthalmoscopic fundal picture may look normal for years, however, although grave functional disorders in photoreceptors are found by electroretinography (Mohamed et al 2003).

LCA is a genetically heterogeneous disease. Clinical phenotypes associated with various genotypes have been intensively investigated during the last few years (Galvin & al 2005; Hanein et al 2006; Yzer et al 2006). Hanein et al (2006) described genotype-phenotype correlations with two clear main groups, i.e. one with congenital or very early cone-rod dystrophy and another with severe progressive rod-cone dystrophy. They also found some additional genotype-phenotype subgroups.

Microarray chips have been developed for LCA diagnostics and genotype-phenotype analyses. Yzer et al (2006) in the Netherlands detected at least four mutation-related clinical groups, i.e. one with early disease and normal fundi, another developing retinitis pigmentosa before the age of 8, a third with relatively normal fundi still at the age of 20–30, and a fourth with distinct fundus abnormalities already at birth (Yzer et al 2006).

Considerable overlapping in phenotypes has been found in some LCA subtypes, which has complicated the specific LCA identification and the counseling of patients on their visual prognosis (Galvin et al 2006). The findings, however, are believed to be beneficial for the possible later development of specific gene therapies.

**Congenital cataract**

Congenital cataract is a relatively common cause of visual impairment in children. It accounts for one-tenth of the cases of childhood visual impairment (Francis & Moore 2004). It is also present in many syndromes and systemic diseases. The incidence of congenital cataract in total has not significantly changed during the last decades (Abrahamsson et al 1999). In a Danish cohort from 1977 to 2001, 1027 cases with congenital/infantile cataract per 2.9 million children were found in children aged 0–17 (Haargaard et al 2005). Males dominated with 62% of the bilateral cases of the cohort. Older maternal age (≥40 years) and a low birth weight (<2000g) were found to be risk factors for bilateral cataract.

In the 1970s till the 1990s, the etiology of bilateral congenital cataract was genetic in around 50% of the cases. In 5–6% of the cases the etiology was prenatal infection, metabolic disorder or other systemic cause, while in
one third or more often it remained unidentified (Rahi et al 2000; Francis & Moore 2004). Autosomal dominant, autosomal recessive, and x-linked modes of inheritance have been identified, and a number of cataract genes and causative mutations have already been characterized (Wirth et al 2002; Reddy et al 2004). The infectious etiology associated with congenital rubella has decreased substantially in Finland after the immunization program for girls commenced in 1975.

The visual outcome of children with severe congenital cataract has improved significantly during the last decades (Francis et al 2001; Lundvall & Kugelberg 2002; Lambert et al 2006). Early surgery, before the age of 6–8 weeks, has led to the best visual results (Lundvall & Kugelberg 2002). Nearly normal visual development has been possible, when treated before the age of three months and cared for with postoperative refractive corrections and orthoptic services (Kugelberg 1992). Secondary chronic glaucoma has been rare and developed predominantly only when the operation was performed during the first week of life (Lundvall & Kugelberg 2002; Lambert et al 2006).

The visual results by early cataract surgery have been further improved by the introduction of intraocular lens (IOL) implantations in the 1980s and by the use of posterior-chamber IOLs since the 1990s (Gimbel et al 1997; Lesueur et al 1998). Some pediatric surgeons have also published good visual results with multifocal IOL implants (Jacobi et al 2001). Poor compliance with occlusion therapy is still the strongest risk factor for low vision (Chak et al 2006; Forbes & Guo 2006).

**Retinopathy of prematurity**

Ocular retrolental fibroplasia (RLF) is the cicatrical end state of retinopathy in preterm children, with total retinal detachment, retrolental fibrous tissue, and blindness. Nowadays it is referred to as retinopathy of prematurity, presenting the most severe blinding stage of ROP. RLF was first described by Terry in 1942. Oxygen support for neonatal asphyxia and respiratory disorders became a form of medical treatment in the 1940s. A correlation was found between the administration of high oxygen levels and the development of RLF in the 1950s, and thereafter, arterial blood gas measurements were taken in use for avoiding RLF in preterm infants. Accurate monitoring of blood oxygen levels by analyzing minute blood samples with micromethods became possible in the 1980s.

The pathogenesis of ROP is not totally known yet. Compared to fetal oxygen levels, oxygen levels in the environment after birth are relatively hyperoxic to infants. Consequently retinal vessels of preterm newborns may constrict to the point of obliteration and free radicals may overwhelm the available antioxidants (Ward & Beachy 2003). The risk for ROP is related to the immaturity of the retinal vasculature and to factors which favor pathological oxygen delivery to the retinal tissue. The development of ROP is initiated and controlled by various angiogenic growth factors providing
oxygen to ocular tissues, e.g. vascular endothelial growth factors (VEGF) and the basic fibroblast growth factor (bFGF) (Phelps 1995; Hellström et al 2001; Hikino et al 2001; Saugstad 2006). In the first phase, hyperoxia inhibits the production of vascular endothelial growth factors, but in the second phase the levels of vascular endothelial growth factors rise and reach critical thresholds around 32–34 gestational weeks, with consequent pathologic retinal neovascularization. Thus, it is possible to prevent the development of severe ROP by avoiding neonatal hyperoxia of preterm infants.

The early classification of ROP was presented by Reese et al in 1953 and a summary of the international classification of ROP has been well presented by Sira et al (1988).

ROP can usually be diagnosed at 32–34 postconceptional weeks. The international classification of ROP describes the location of pathologic changes in concentric rings relative to the optic nerve (Zones I, II, III), to the stage of abnormality, to the extent of developing blood vessels (according clock hours), and to the presence of plus disease, when engorged and tortuous vessels are present (Committee for the Classification of Retinopathy of Prematurity 1984). Retinal changes in ROP are graded into stages 1–5 by the severity of retinopathy, from a white demarcation line in stage 1 to total retinal detachment in stage 5. Threshold ROP is defined as stage 3 in Zone I or II with five contiguous or eight non-contiguous clock hours. Without treatment threshold ROP leads to retinal detachment in more than 50% of cases. Plus disease is a serious sign of severe retinopathy and often leads to retinal detachment.

**Prevalence of ROP**

The prevalence of ROP increased in western countries in the 1980s due to the higher survival of very immature infants, but since the 1990s the incidence and severity of ROP has declined along with improvements in the neonatal intensive care (Fielder et al 1992; Rosenberg et al 1996; Jacobson 1998; Hussain et al 1999; Fledelius et al 2000; Termote et al 2003).

According to Maly (1993) in Malmö, Sweden, ROP was diagnosed in 1986–1990 in 19% of the infants with a birth weight (BW) <1501g or born at <33 gestational weeks (GWs) and in 40% of the infants with a BW <1000g or born at <29 GWs. According to Jacobson et al (1998) in Stockholm, all children blinded due to ROP in 1980–1990 in Sweden were born at <31 GWs.

In western Norway, the ROP incidence in 1989–1993 was 10% in infants with a BW <1500g (Haugen & Markestad 1997). ROP stage 3 was only seen in 3% of their study group, and more severe stages were not found at all.

In the 2000s, ROP seems to be rare in western children with a BW >1500g or born at a GA >32 weeks. Blindness due to ROP seems to be confined mainly to the infants with a BW <1000g (Larsson et al 2002; Allegaert et al 2003).
**Risk factors for ROP**

ROP appears to be a multifactorial disease and various potential risk factors have been described (Maly 1993; Nödgaard et al 1996; Holmström et al 1998; Hussain et al 1999; Seiberth & Linderkamp 2000; Larsson et al 2002; Ward & Beachy 2003). Gestation age is the key factor correlating with the risk for ROP. Neonatal asphyxia, acidosis, bronchopulmonary dysplasia (BPD), duration of oxygen treatment, repeated blood transfusions, and hypothermia are risk factors for ROP. Seiberth and Linderkamp in Germany (2000) found that a LBW of ≤1500g, artificial ventilation over 7 days, high volume of blood transfusion, and maternal pre-eclampsia were independent factors for ROP. Allegaert et al found in the Belgian EpiBel cohort in 1999–2000 (2004), that renal insufficiency (serum creatine >1.5 mg/dl) was a risk factor for threshold ROP in extremely low birth weight (ELBW) infants born at 22–26 GWs.

**Prevention of ROP**

The international ROP committee issued guidelines for the ROP classification and the screening of preterm children in 1984 (Committee for the classification of Retinopathy of Prematurity 1984). A joint statement for the ocular screening program for detecting infants at ROP risk was reissued by the American Academy of Pediatrics, the American Association for Pediatric Ophthalmology and Strabismus, and the American Academy of Ophthalmology in 1997.

The retinal screening of preterm infants has to be started at 4–6 weeks of life or between 31–33 GWs (the sum of the gestational and postnatal weeks). The follow-up has to be carried out at 2 week intervals until the retinal peripheries have been vascularized (approximately at 4 months). ROP is an aggressive angiogenetic disorder, but it may subside spontaneously without treatment (Mechoulam & Pierce 2003). When necessary, treatments are used for destroying the abnormal avascular retinal tissue, in order to prevent the growth of abnormal blood vessels and the vision-threatening scar tissue formation.

**Treatment for ROP**

Treatments for ROP were started with xenon light coagulation by Nagata in 1968 in Japan. Trials with cryo therapy were started in the beginning of the 1970s and cryo therapy was accepted for general use in the 1990s after an extensive and highly-qualified American multicenter study (Cryotherapy for Retinopathy of Prematurity Cooperative Group 1988, Cryotherapy for Retinopathy of Prematurity Cooperative Group 1990). Trials with laser therapy were also started at the end of the 1980s and successful results were achieved by combining cryo and laser therapy (Laatikainen et al 1995). Laser therapy is less irritating and causes less pronounced scars than cryo coagulation, but the treatment of the most anterior retina with laser may
sometimes be difficult (Laatikainen et al 1995). Consequently, combined laser and cryo treatment was recommended for use in Finland at the time (Laatikainen 1995).

During the last ten years, the outcomes with laser therapy for threshold ROP have been excellent. During the 2000s, favorable anatomic and functional outcomes have been achieved in nearly 100% of the eyes treated with laser photocoagulation for threshold ROP, while unfavorable anatomic outcomes have been fewer than in the cases treated with cryo therapy (Foroozan et al 2001; The Early Treatment for Retinopathy of Prematurity Cooperative Group 2003; Jandeck et al 2005; The Early Treatment for Retinopathy of Prematurity Cooperative Group 2006; McLoone et al 2006).

Retinal ablative therapy has to be started for eyes with any stage of ROP in zone I with plus disease and for eyes with stage 3 ROP in zone I without plus disease. For eyes with threshold ROP, the treatment has to be arranged within 3 days. High risk infants with prethreshold disease have to be followed at weekly intervals, because a threshold stage may appear before 31 GWs in ELBW infants. In very young infants, the screening criteria may need to be modified further.

Nowadays, a progress to retinal detachment is rare in children born at >28 GWs or with a BW >1000g. Long supplemental oxygen therapy, however, may lead to ROP stages 4–5, and unfortunately, very aggressive posterior ROP in ELBW infants may be unresponsive to conventional treatments (Hussain et al 1999; Quiram & Caponen 2007). Surgical results have improved during recent years (Lakhanpal R et al 2005). The functional outcome after retinal detachment due to ROP is, however, still poor (Repka et al 2006).

**Cerebral visual impairment**

Mainly due to the improved survival of premature infants during the last decades, cerebral cortical and subcortical disorders are rapidly becoming the leading cause of bilateral visual impairment in western children (Good et al 2001; Edmond & Foroozan 2006). Most cases of cerebral visual impairment (CVI) in full-term and preterm children arise from prenatal and perinatal cerebral hypoxic-ischemic injuries (Dalens et al 2006; Fazzi et al 2007). Other causes of CVI are e.g. encephalitis, meningitis, metabolic disorders, hydrocephalus, and head trauma (Huo et al 1999).

In preterm children brain disorders tend to selectively injure cerebral subcortical white matter, resulting in periventricular leukomalacia (PVL) (Brodsky et al 2002). PVL is often initiated by perturbations in cerebral blood flow and by cerebral intraventricular hemorrhages in very immature infants (Volpe 2001; Ward & Beachy 2003; Back 2006).

The principal cognitive visual pathways of the brain comprise the dorsal and ventral routes (Dutton & Jacobson 2001). Injuries in these pathways lead to a variety of combinations of visual disorders. Lesions in cerebral white and grey matter may occur without afflictions in the anterior visual
pathways, but they may be simultaneously affected (Dutton & Jacobson 2001; Andersson et al 2006). Magnetic resonance imaging is the diagnostic method of choice, and normal MRI findings usually correlate with normal vision (Uggetti et al 1996).

PVL occurs in 65% of the prematurely born children with visual impairment (Jacobson 1998). In a Finnish study in Oulu, the prevalence of PVL was 32% of preterm children, but none of the term children had the disorder (Olsen et al 1997).

Cerebral visual dysfunction caused by PVL is characterized by delayed visual maturation, subnormal visual acuity (VA), defects in visual fields and accommodation, crowding phenomenon, other visuo-perceptual problems, abnormal visual behavior and visual inattention (Cooke et al 2004b; Fazzi et al 2004).

Alterations in the oculomotor functions may include roving eye movements, nystagmus, lack of gaze coordination, inability of fixation and tracking of objects, tonic gaze deviation, gaze palsies, and oculomotor apraxia (Weiss et al 2001; Andersson et al 2006). Visual acuity may be difficult to evaluate, because ocular motor disorders lead to abnormal visual behavior (Good 2001).

Visual disorders may include difficulties with moving through various levels of depth, perception of movements, recognition of objects and persons and simultaneous perception. Falling on stairs, bumping into obstacles, and getting lost in familiar surroundings are associated with these neuro-ophthalmological disorders (Salati et al 2002).

Children with CVI often have a short visual attention span and their visual performance may vary from time to time. They see better in familiar surroundings and when they are relaxed and well rested. They often use peripheral vision to search for objects and they may turn their head away from objects before reaching out for them. Photophobia is present in a third of the cases, although they gaze at lights from time to time.

Most children with CVI remain visually impaired, but in favorable circumstances the neuroplasticity of the visual system leads to some degree of reintegration and visual recovery in most cases. The results of rehabilitation have been encouraging, even in such cases where the early initial vision has only been at the level of light perception (Huo et al 1999; Good et al 2001; Malkowicz et al 2006; Matsuba & Jan 2006; Fazzi et al 2007).

**Colobomata**
The prevalence of coloboma is approximately 7/100,000 births according to western registers on congenital malformations. Choroidal, iris, and optic nerve colobomata originate from various causes, within the first month of the embryonal life. Some are genetic, but the etiology often remains unknown. Colobomata may be combined with other ocular malformations, e.g. microphthalmos, microcornea, vascularized cornea, lens opacity,
congenital aphakia, or ectopic lens. They may also be associated with systemic malformations (Hornby et al 2003; Fahnehjelm 2003).

The influence of colobomata on visual capacity depends on the site and the extent of anomalous areas. Only some of the afflicted children are visually impaired. Children with associated systemic malformations are more likely to be mentally retarded than those with solitary ocular anomalies.

The prevalence of retinal detachment may be as high as 23%-43% in colobomatous eyes, and therefore, prophylactic therapy and surgery for retinal detachment may be needed (Daufenbach et al 1998).

**Optic nerve hypoplasia**

The prevalence of optic nerve hypoplasia (ONH) is approximately 2–6/100,000 (Blohmé et al 1997). ONH is a congenital developmental disorder due to various causes. Neonatal hypoglycemia (43%) and prenatal exposure to teratogens (18%) has been found in children with ONH (Fahnehjelm et al 2003). A quarter of the involved children have endocrinological abnormalities, due to septo-optic dysplasia and panhypopituitarism (Siatkowski et al 1997; Fahnehjelm et al 2003). ONH may also be associated with other severe malformations in the central nervous system (Tornqvist et al 2002).

The hypoplastic optic nerve is small in diameter and does not provide normal visual functions. The majority of the children with optic nerve hypoplasia are practically blind (WHO categories 3–5) according to the Finnish Register of Visual Impairment (Ojamo 2006).

**Aniridia**

Aniridia is a congenital genetic disorder of the iris development with the autosomal dominant mode of inheritance in the majority of cases. In the Nordic countries, the prevalence of aniridia is approximately 1/70,000. The prevalence of visual impairment in cases with aniridia is around 4/100,000 (Blohmé & Tornqvist 1997b).

The primary visual development of children with total or partial aniridia always remains abnormal and typically they are partially sighted (WHO categories 1–2) according to the Finnish Register of Visual Impairment (Ojamo 2006). Most frequently, aniridia is an isolated ocular anomaly, but it may be associated with systemic diseases, e.g. with kidney defects.

Visual acuity and visual comfort of children with aniridia can be improved by an iris device implantation (Menezo et al 2005). The implantation of an artificial iris seems to be safe and efficient, although some risks of postoperative glaucoma exist (Mavrikakis et al 2005). Corneal clouding, cataract, and secondary glaucoma are relatively common later problems in children with aniridia.
Etiology of visual impairment in children

Genetic factors, infections, maternal chronic diseases, pre-eclampsia, prenatal and neonatal asphyxia, and exposures to tobacco, alcohol, and teratogenic medicines have been common and serious etiologies of visual impairment in children during the last three to four decades in Europe. Approximately 75% of the causes have not been preventable or treatable and the main causes have been prenatal and perinatal (Rahi et al 2003).

Since the 1960s, the distribution of various etiologies has remained rather equal, i.e. prenatal influence in 40%–65% (including genetic factors in 25%–50%), perinatal causes in around 20%, postnatal causes in around 15%, and a lower number of totally unknown causes (Copper & Schappert-Kimmijser 1970; Crofts et al 1998; Rahi et al 2003). Also in the Nordic incidence study, prenatal and perinatal causes were found at the same rates, i.e. prenatal etiology in 64% (including genetic factors in 27%) and perinatal etiology in 21%, but infantile-juvenile causes had occurred in 9% and unknown causes in 6% (Rosenberg et al 1996). In a Swedish doctoral thesis by Jonas Blohmé in Lund in 2000, the results did not differ significantly, and the infantile-juvenile etiology was present in 7% (Blohmé & Tornqvist 1997c). Prenatal unspecified causes were recorded in 28% and prematurity in 11% in that Swedish survey.

Genetic etiology

During the last three to four decades, the etiology of visual impairment in children has been genetic in more than 25%–50% of the cases in western studies (Lindstedt 1972; Schappert-Kimmijser et al 1975; Forster 1988; Rogers 1996; Rosenberg et al 1996; Rahi et al 2003).

The ocular development during pregnancy is determined mainly on a genetic basis. Retinal differentiation begins around the 47th day of gestation, and cones and rods can be distinguished at the 15th gestational week. Retinal development continues until the 8th month and the fovea becomes fully functional after birth. At the 7th gestational month, the axons of the optic nerve become myelinated. The optic nerve is 3 mm thick at birth and its diameter continues to increase for 6–8 years after birth.

Alterations in the genetic programming of the eye by gene mutations may lead to severe disorders. One half of the blindness in children has a genetic etiology (Graw 2003). New spontaneous gene mutations occur unexpectedly among children born to healthy parents (Nelson & Holmes 1989). Mutations in two genes have been shown to be necessary for some diseases, but for others even a third sequence alteration is not sufficient. Modifier genes have been recognized as an important source of phenotypic variation. Genetic modifiers may influence e.g. on the age of the onset, the progression rate, or the severity of the disease. These background genes interact with the disease mutation leading to specific phenotypes (Haider et al 2002).
Some genes have mutations that affect the anterior segment of the eye, while others interfere with the development of the lens, the retina, or the optic nerve (Graw 2003). Some genetic disorders are associated with chromosomal defects and congenital malformations. The European Surveillance of Congenital Anomalies (EUROCAT), a network of population-based registries on congenital anomalies in Europe, suggests that over 15% of cases with microphthalmia and anophthalmia are caused by chromosomal abnormalities (Morrison et al 2002). Cortical malformations may also have a genetic basis (Gaitanis & Walsh 2004).

**Prenatal etiology**

*Infectious etiology*
The infectious agents during pregnancy may be cytomegalovirus (CMV), herpes simplex virus (HSV type 1 and HSV type 2), varicella zoster virus, parvoviruses, chlamydia, group B streptococcus, neisseria, various other bacteria, trichomonas, toxoplasma gondii, etc. Fetal infections during the 4th–14th GWs pose serious risks for the fetal development (Ornoy & Diav-Citriun 2006; Pass et al 2006).

Most maternal infections arise from the vagina or the urinary tracts and may lead to chorioamnionitis. Also in asymptomatic pregnancies terminating at full term, intrauterine infections may cause fetal growth retardation, microcephalus, hydrocephalus and developmental disorders of various organs including eyes and visual pathways (Shalak & Perlman 2002; Shalak et al 2002). Infections, even dental ones, should be screened for and treated carefully, preferably already prior to the pregnancy.

Neonatal HSV infections in infants are not common (1 in 3,500–20,000), but they may lead to severe infant morbidity (Kesson 2001). Treatment with acyclovir is recommended, when a HSV infection has been diagnosed during pregnancy (Vasileiadis et al 2003). A cesarean section is necessary, when active virus lesions are present on the genitals at the time of the labor.

After varicella zoster infections microphthalmia, congenital cataract, optic nerve atrophy, developmental delay, and epilepsy occur. Of the infants infected with human immunodeficiency virus, 15%–20% will have serious encephalopathy.

Bacterial vaginosis occurs in 10%–30% of cases. Its treatment is problematic, because efficient antibiotic medication is not available (McDonald et al 2005). Likewise, efficient treatments for cytomegalovirus infections still need to be researched for.

*Other prenatal etiologies*
Maternal chronic diseases (i.e. diabetes, asthma, epilepsy, rheumatoid arthritis, systemic lupus erythematosus (LED), hemophilia, and other severe systemic diseases) may be responsible for visual impairment in
children. The medication for systemic diseases and infections may cause disorders of the embryogenesis, also leading to malformations and visual impairment (Malm 2002).

Pre-eclampsia is a risk factor for visual impairment in full-term children (Tornqvist & Källen 2004). Pre-eclampsia (i.e. systemic blood pressure >140/90 and proteinuria >0.5 g/day) is a serious disease of the placenta with general reduced tissue blood flow and tissue edema. The disorder may lead to convulsions, cerebral and pulmonal edema, and even to fatal states. The basic cause of its origin is still unclear, but maternal infections, systemic blood pressure, dyslipemia, obesity, diabetes, and many other risk factors for the health increase the risk for pre-eclampsia (Pöyhönen-Alho et al 2005). The incidence of pre-eclampsia has been 8%–10% and the incidence of severe pre-eclampsia requiring hospital treatments around 2% in the Finnish pregnancies (Gissler et al 1996). Delivery is the only effective treatment available for the prevention of serious complications.

The human placenta has a crucial role of supplying the fetal metabolism (Miller et al 1993). The placenta also metabolizes harmful substances into ones less toxic for the fetus, prior to transferring the metabolites into the fetal circulation. Placental insufficiency with alterations in blood flow and reductions in the transfer of nutrients afflicts the fetal growth and development.

Fetal asphyxia is dangerous to the nervous cells and the vital organs of the fetus. During asphyxia, the fetus suffers from lack of oxygen, retention of carbon dioxide, and ischemia (Fellman & Herrgård 1996). The disorder is usually long-lasting, associated with placental insufficiency. The risk for asphyxia is increased e.g. due to maternal chronic diseases, medications, pre-eclampsia, and multipregnancies. Asphyxia can be classified into 3 categories according to Apgar scores: moderate (Apgar scores 5–7), severe (Apgar scores 3–4), and profound (Apgar scores 0–2). Nowadays the severity of asphyxia has been mainly defined by the umbilical arterial blood pH factor. A pH factor of <7.2 always indicates fetal stress and signals a considerable risk of encephalopathy.

Smoking as well as exposure to environmental tobacco retard the fetal growth and increase the risk for preterm birth. Harmful effects have usually remained marginal, if smoking has been stopped as soon as the pregnancy has been identified (Chiolero et al 2005; Morken et al 2005). Smoking is responsible for 15% of all preterm births and it has a considerable influence on the overall perinatal mortality (Andres & Day 2000). According to Jaakkola et al (2001), smoking during pregnancy has not decreased in Finland in the 1980s and 1990s. In the southern and western Finland the prevalences of smoking have been highest (25%–37%).

Alcohol increases the risk for fetal growth retardation, congenital malformations and preterm delivery. Drinking during the first months of
pregnancy has curvilinear effects on the fetal development (Lundsberg et al 1997). The incidence of the fetal alcohol syndrome (FAS) is 100–200/100,000 or more in western countries and the number of infants with fetal alcohol effect (FAE) is at least double (Halmesmäki & Autti-Rämö 2005). All parts of the eye may be involved in FAS. Microphthalmus, microcornea, Peters’ anomaly, cataract, persistent hyperplastic primary vitreous, colobomata, retinal dysplasia, and optic nerve hypoplasia occur in FAS (Strömland 2004).

**Perinatal etiology**

The proportion of perinatal etiology has been around 20% in various studies during the the 1990s and 2000s. Perinatal asphyxia, arterial hypotension, and infections, including infant sepsis, lead to severe neurological morbidity and increased infant mortality in preterm and full-term infants (Thorngren-Jerneck & Herbst 2001).

Likewise, metabolic disturbances in the perinatal period lead to serious consequences, e.g. neonatal hypoglycemia (<1.5 mmol/l during the first 3 days) may cause occipital brain injuries with consequent cerebral visual impairment (Brodsky et al 2002; Fahnehjelm et al 2003; Inder et al 2003; Filan et al 2006). The extent of the cerebral damage relates to the state of the brain development at the time of birth.

In hyperbilirubinemia the neurotoxicity of bilirubin has been well established and neonatal serum bilirubin levels of infants are followed up carefully in Finnish neonatal care units (Grönroos 2007). Too high bilirubin levels (≥340μmol/l) are prevented by early phototherapy with blue-green light or by blood transfusion in severe cases. The risks for visual impairment due to hyperbilirubinemia have not been clearly verified, but premature infants are probably more susceptible to bilirubin encephalopathy (kernicterus) than full-term infants.

**Prematurity as the cause of visual impairment**

The definition of prematurity was based on low birth weight (LBW) prior to the ultrasound period, i.e. BW <2500g was used as the criterion of prematurity. Nowadays, infants born at a GA <37 weeks are defined as preterm.

The prevalence of preterm births in Finland was 9% in the 1960s and decreased to the level of 5% in the middle of the 1980s. According to the Perinatal Statistics of the National Research and Development Centre for Welfare and Health (Stakes) published since 1987, the birth rate of preterm infants has been 4%–5% and that of very preterm infants (GA <32 weeks) around 1% (Koskinen et al 1999).

A slight increase in preterm births from 5.0% up to 5.3% has, however, been seen during the latter half of the 1990s (Koskinen et al 1999). Slight
rises in preterm birth rates from the 1980s have also been reported in some other western countries, due to the higher survival rate of very immature infants (Stoelhorst et al 2005).

The causes of prematurity are not thoroughly understood and the efficient prevention of preterm births is not possible. In the 1950–1960s, the outcome of LBW infants was very poor and the rate of visual impairment in LBW children was 60%. From the 1960s through the 1980s, the incidence of disability in LBW infants seemed to decrease in some countries, e.g. in Canada (Saigal et al 1989). Along with the higher survival of ELBW infants, the rates of morbidity started to increase in the 1990s in many countries (Escobar et al 1991; Vohr et al 2000; Tommiska et al 2001).

The development in the neonatal intensive care has also gradually led to a better prognosis for VLBW infants. The possibilities for the prevention of ROP improved essentially during the 1990s due to accurate monitoring devices for hypoxia and improved controlling of arterial oxygenation in neonatal patients. Antenatal treatments with glucocorticoids and surfactants since the 1990s improved the respiratory function of very preterm infants and decreased their morbidity (The Victorian Infants Collaborative Study Group 1997; Tommiska et al 2001; Weber et al 2005; Wilson-Costello et al 2005). Neonatal infections, however, have been frequent complications in ELBW infants in intensive care units and are associated with poor neurodevelopmental and growth outcomes in the early childhood (Holcroft et al 2003; Stoll et al 2004).

Periventricular leukomalacia is the major neuropathologic form of a preterm brain injury (Volpe 2001; Back 2006). Periventricular injuries are initiated by perturbations in the cerebral blood flow, which reflect anatomic and physiologic immaturity of the vasculature. Postnatal acidosis, asphyxia, and thrombocytopenia in preterm infants associate with neonatal intracerebral hemorrhages. The development of PVL with periventricular cystic cavities, gliotic scarring, and dilated lateral ventricles of the brain is dependant on the degree of prematurity and the metabolic activity of the infant. High rates of cerebral palsy (78%), mental retardation (72%), and epilepsy (56%) have been diagnosed in the preterms with intraventricular hemorrhages and posthemorrhagic hydrocephalus (Fernell et al 1994).

**Infantile-juvenile and other etiologies of visual impairment**

Nowadays, a relatively small proportion of childhood visual impairment is caused by infantile-juvenile causes, such as infectious diseases, diseases in the central nervous system, head traumas, or other specified disorders. In some cases, the etiology of visual impairment may still remain unknown by time and cause.
Multiple impairment in children with visual impairment

Severe motor and cognitive impairment is common in children with visual impairment. Multiple impairments were present in 50% of the blind children born from 1945 through 1984 in British Columbia in Canada (Robinson et al 1987). During that study period, the blindness due to maternal rubella infections decreased progressively since the early 1960s, although most children with congenital cataracts remained blind. Instead, the incidence of multihandicapped children with optic nerve atrophy, optic nerve hypoplasia, and ROP increased gradually since the middle of the 1970s.

Along with improvements in the neonatal intensive care and the higher survival of VLBW infants, the prevalence of children with visual and other impairments has increased during the last two to three decades (Flanagan et al 2003). Rosenberg et al (1996) in the Nordic countries described an increase from 30%–50% in the 1970–1980s to 61% in 1993 for children with visual and additional impairment. Cerebral palsy and epilepsy were the most common systemic diseases in those children with multiple handicaps.

Of the Swedish children with visual impairment, born in the 1970–1980s, 60% had an additional impairment, including mental retardation in 50%, motor impairment in 37%, and auditory impairment in 8% of the cases (Blohmé & Tornqvist 1997c; Blohmé 2000). In children with perinatal etiology of visual impairment, additional impairment was present in 83% and it was even more pronounced in the full-term children than in the preterms. The perinatal period was found to be the most dangerous period for severe ischemic brain injuries and multiple handicaps both in full-term and preterm births.

In the 1990s, the incidence of multiple handicaps has inversely correlated with birth weight and gestational age (Tommiska et al 2001; Cowan et al 2003; Stoelhorst et al 2005). In southern Germany in 1990–1993, the incidence of children with visual and other impairments was 67/100,000. The children had severe neurological impairment with motor disorders in 80%, epilepsy in 67%, and cerebral palsy in 66% of the cases (Häussler et al 1996). Equivalent results were also detected in a large American study on ELBW infants (BW 401–1000g) born in 1993–1994, with a 9% rate of visual impairment and a high frequency of intraventricular hemorrhages and posthemorrhagic hydrocephalus (Vohr et al 2000).
Congenital malformations in children with visual impairment

Prevalence of congenital ocular and other malformations
National registries for congenital malformations are maintained in many western countries. The prevalence of all congenital malformations varies between 1.5%–7.5% (Kennedy et al 2004; Gilbert 1999). In Spain, the prevalence of congenital ocular malformations is around 37/100,000 (Bermejo & Martinez-Frias 1998). The corresponding prevalence in France is 68/100,000, and those for congenital cataract 27/100,000, microphthalmia 17–20/100,000, coloboma 10–14/100,000, and for anophthalmia 2/100,000 (Stoll et al 1997). The prevalences of congenital ocular malformations are nearly equal in many western countries. In cases with combined microphthalmia, coloboma, and anophthalmia, the prevalence was 19/100,000 in Scotland in the 1980s (Morrison et al 2002).

In Finland, the incidence of congenital malformations was first examined in the 1960s by Klemetti (1966) and the malformation rate of children born in Central Finland was 3%. The Finnish annual incidence for congenital malformations has also remained stable at 3%, according to the Finnish Register on Congenital Malformations in the National Research and Development Centre for Welfare and Health (Stakes).

Etiology and risks of visual malformations
The most susceptible period for the induction of malformations is the period from the 2nd through the 14th week of gestation. The etiology is genetic in approximately 20%–25% of cases and chromosomal in 5%–10%. Genetic factors also influence the fetal cortical development (Gaitanis & Walsh 2004; Mochida & Walsh 2004). Maternal health disorders, infections, various environmental factors, and exposures to teratogenic agents are responsible in 5%–10% of the cases. In more than 50% of the cases, the etiology remains unknown (Brent & Beckman 1990; Bishop et al 1997; Seaver 2002; Graw 2003).

The use of alcohol during pregnancy may cause serious fetal alcohol effects (FAE) or fetal alcohol syndrome (FAS). The rate of FAE is at least two to three times higher than that of FAS. The incidence of FAS is 100–200/100,000 or higher for live births in western countries. Infants with FAS are small in size and have CNS involvement, typical anomalous faces with short palpebral fissures, microcephali, anomalies in many organs, and ocular malformations. Ocular malformations include e.g. microphthalmus, microcornea, Peter’s anomaly, colobomata, cataract, persistent hyperplastic primary hyaloid, retinal dysplasia, and optic nerve hypoplasia (Strömland 2004). Risks for fetal alcohol effects can be diminished significantly by stopping the use of alcohol as soon as the pregnancy has been noticed.
According to recent opinions, less than 1% of all human malformations are related to drug exposure, chemicals, and radiation (Brent 2004). The dose is a crucial factor for the toxicity (Bishop et al 1997). Each teratogen has a threshold dose, below which no risks for malformations exist. Some safe medicines may also be teratogenic, if overdosed (Bishop et al 1997).

The identified side effects of drugs are reported by physicians in Finland and they are analyzed by the National Agency for Medicines in Helsinki. Most maternal drugs are transferred to the fetus. Penicillins and erythromycin are safe chemotherapeutics, also used during pregnancy. Antidepressants, lithium, long-acting benzodiazepines, barbiturates, indomethacine, new antiepileptic drugs (especially valproate), chloramphenicol, metronidazole, tetracyclines, trimethoprim, tretinoins, and new drugs in general should not be used during pregnancy (Malm 2002).

Regular nutrients may include risky substances for the fetus, e.g. excessive levels of vitamin A may produce teratogenic metabolites (tretinoins) and induce fetal maldevelopment (Miller et al 1993; Malm 2002). Alcohol, tobacco, and poor nutrition are often combined and thus several exogenic factors may influence simultaneously.

Maternal and paternal age may have negative effects on the general and visual outcome of pregnancy. Teenagers and women >35 have a general increased risk for giving birth to children with congenital malformations (Abel et al 2002). Older maternal age associates with increased rates of chromosomal anomalies (Chervenak & Kardon 1991). Older paternal age (≥50) associates with some hereditary diseases, e.g. with several x-linked recessive and autosomal dominant diseases (McIntosh et al 1995; Plas et al 2000; Glaser & Jabs 2004). In British Columbia, of 9660 cases of registered malformations, an older paternal age associated with increased risk for neural tube defects and congenital cataracts. Glaser et al (2003) found increased sporadic cases of Apert syndrome in cases with advanced paternal age (Glaser et al 2003). The American Fertility Society recommends an age limit of 50 years or less for semen donors.

**Prevention of congenital visual malformations**

Ultrasonographic scanning (US) techniques have been developed for the obstetrical use. In Finland, US screenings for congenital malformations are now performed twice during pregnancies, first at 11–13th GWs and then at 18–20th GWs. In difficult cases, magnetic resonance imaging is used for more accurate findings (Vergani et al 1994; Blaicher et al 2003).

Teratologic information services have been provided by the Family Federation of Finland in Helsinki since 1994, in co-operation with Nordic and other European teratologic services.
Mortality of children with visual impairment

According to the Statistical Yearbook of Finland 2001, the perinatal and juvenile mortality rates have decreased continuously from the 1920s in Finland, as in most developed countries (Häussler et al 1996; Arnaud et al 1998). The mortality has been somewhat higher in boys than girls.

In Finland, the mortality rates in children aged 0–4 were 2.1/1000 children in 1976–1980 and 1.4/1000 children in 1985–1990. In children 15–19 the mortality was 0.7/1000 during both periods. The mean annual death rates at the age of less than one year were 9.4/1000 children in 1971–1980, 9.6/1000 in 1981–1990, and 9.7/1000 in 1991, i.e. the juvenile child mortality during the first year of life was 1% in 1991.

The mean annual numbers of the children that died under one year old were 611 in 1971–1980, 376 in 1987–1990, 251 in 1995, and 181 in 2001. The perinatal mortality (i.e. stillbirths and deaths during the first week of life) in Finland has diminished successfully from around 9/1000 births in 1987 to 7/1000 births in 1998 (Koskinen et al 1998; Koskinen et al 1999). In multiple births, the mortality has been significantly higher, possibly due mainly to the lower birth weight distribution among twins and triplets (Imaizumi 2001). The mean perinatal mortality in 1991 was 51/1000 in twins and 13/1000 in triplets.

In the beginning of the 1990s, the perinatal mortality was significantly higher in preterm children, i.e. 1000/1000 in infants at GA 21 weeks, 547/1000 at GA 22–28 weeks, 212/1000 at GA 29–31 weeks, and 37/1000 at GA 32–36 weeks. According to the birth weights, the perinatal death rates were 964/1000 in children with BW <500g, 573/1000 with BW 500g–999g, and 208/1000 with BW 1000g–1499g. In children with GA 38 weeks or with BW ≥2500g, the perinatal mortality rates equaled the mean annual rate.

The main causes of perinatal death in Finland in 1980–1985 were congenital malformations, asphyxia, and preterm deliveries (Raivio 1990; Erkkola & Kero 1991). Preterm birth has been responsible for 75%–90% of all neonatal mortality not associated with congenital malformations. In extremely low birth weight (ELBW) infants, the main causes of death have been pulmonary problems and infections. Congenital malformations are still responsible for about 15%–20% of all infant deaths in western countries.

A significant decrease in the overall mortality of very preterm infants has been evident in the 1980–1990s and a drop in infant mortality from the level of 75% to around 30% has been seen in births before 27 GWs. A Swedish study on the survival of ELBW infants during 1986–1994 discovered a rise from 47% to 70%, and in the cases without bronchopulmonary dysplasia or major intracranial hemorrhages the percentage of the survivors rose from 67% to 87% (Svenningsen et al 1997).
Mortality in children with visual impairment is higher than in the child population in general (Blohmé and Tornqvist 2000; Rahi et al 2003). In Swedish children with visual impairment, born from 1962 through 1976, the mean mortality rate was 13%, which was 60 times higher than in the general Swedish child population. In the Swedish cases with severe visual impairment (VA <0.05) and an additional impairment, the mortality rate was as high as 36%, while a 11% mortality rate was seen in the group of less severely impaired children. In England, 10% of the children with severe visual impairment or blindness died within one year from the diagnosis of blindness (Rahi et al 2003).

Rehabilitation for visual impairment in children

After lesions in visual pathways and cerebral cortex, the brain may adjust to modifications in the sensory environment resulting in some improvements in perceptual skills and sensorimotor performances (Safran & Landis 1999; Yao et al 2004). Although the modifications in intracortical connections and the cortical rearrangement do not restore the function of destroyed tissues they help to compensate for gaps in perception. Obvious visual recovery has also been reported after visual stimulation programs in children with severe cerebral visual impairment due to injuries affecting optic radiations and visual cortex (Malkowicz et al 2006).

Infants may be visually unresponsive despite having normal ocular structures (Weiss et al 2001). The goal of visual rehabilitation is to maximize the use of the residual vision. In the majority of cases, visual functions can be improved by visual activation and stimulation, by the use of low vision devices and by visual training with methods individually applicable in each particular case (Salati et al 2002; Maurer et al 2005; Markowitz 2006).

Some methods have been efficient, e.g. the use of simplified visual environments during visual tasks, the use of motion for facilitating visual perception, and the reinforcement of the learning process with lights, sounds, and tactile stimuli. Weak visual functions are strengthened with regular training tasks, e.g. tasks for fixation and other eye movements and for tracking objects at various distances (Salati et al 2002). The ritualization of tasks performed in the same way at the same time for longer periods may be beneficial.

The visual prognosis can often be improved with early intervention. The results point to some neuroplasticity in the visual systems, even in severe encephalopathies. Pediatric ophthalmologists and neurologists, neuroradiologists, and psychologists are often indispensable on multidisciplinary teams for the rehabilitation of children with visual impairment (Bothe et al 1991; Good et al 2001; Jacobson et al 2004).
Prospects of childhood visual impairment

**Gene therapy for inherited diseases**

Gene therapies are now investigated intensively by using animal models and virus vector mediated gene transfers. The aims are to correct human genetic defects with gene transfer or overexpress proteins that are therapeutically useful (Rubanyi 2001). Intravitreal and subretinal injections for adeno-associated virus (AAV) mediated gene transfer have shown to benefit eyes and visual pathways. Thus, they have given the promise of treatments for monogenic eye diseases in the future (Fazzi et al 2003; Frigg et al 2005; Griffey et al 2005; Yokoi et al 2007). Possibilities for fetal gene therapy have also been researched (Coutelle et al 2005).

AAV mediated gene transfers have already been able to establish retinal functions in Leber’s congenital amaurosis, and human clinical trials have started (Fazzi et al 2003; Frigg et al 2005). In x-linked juvenile retinoschisis, a highly specific AAV5-opsin promoter vector has been used in a mouse model, progressive improvements in retinal functions and morphology have followed (Min et al 2005). In infantile neuronal ceroid lipofuscinosis, deficient enzyme activities have been increased by intravitreal injections of the known enzyme by using AAV vectors. Consequent improvements in retinal cone and rod functions have been recorded (Griffey et al 2006).

**Research on therapies with stem cells and antiangiogenetic agents**

Human embryonic stem cells are capable of self-renewing in cultures and can principally specialize for any adult cell function. In mice and embryonic chick eyes, subretinally injected retinal stem cells have been able to survive, migrate, integrate and differentiate into the neural retina, even into photoreceptors.

It has now been suggested, that human embryonic retinal stem cells or slightly further differentiated cells may eventually be used for the treatment of human retinal diseases (Coles et al 2004; Bartsch et al 2005; Haruta 2005). Some predifferentation before the transplantation may be necessary for obtaining the graft integration into the degenerating outer nuclear layer of the retina (Canola et al 2007). A critical stage for the transplantation of photoreceptor precursor cells has been identified in mice models for retinitis pigmentosa, and appropriate cells for the transplantation now need to be generated.

A human neural stem cell product is under investigations as a potential treatment for neuronal ceroid lipofuscinosis. A phase I trial of the product for infantile and late-infantile NCL has been initiated (Taupin 2006). The ROP progression into threshold ROP may possibly be prevented in the future by blocking the excessive production of vascular endothelial
growth factors (VEGFs) with specific anti-angiogenic agents, which do not interfere with the normal angiogenesis (Cooke et al 2004a).

**Research on encapsulated cell technology**

Encapsulated cell technology allows long-term administrations of protein drugs to the eyes without systemic exposures, e.g. a ciliary neurotrophic factor has shown to protect the retina from degeneration in animal models (Tao 2006). The effectiveness and the safety of neurotrophic implants in retinitis pigmentosa and other retinal degenerations are presently under intensive investigations.
THE AIMS OF THE STUDY

Our purpose was to examine the prevalence, causes, and profile of visual impairment in Finnish children and their possible changes from 1972 through 1989.

The specific aims were:

1. To develop a new standardized classification system for visual impairment in children, especially for coding diagnoses, etiologies, and multiple impairment.

2. To study the prevalence and the causes of visual impairment in Finnish children born at full term and prematurely from 1972 through 1989.

3. To investigate the morbidity of Finnish children with visual impairment.

4. To search for risk factors of visual impairment in children, with special attention to further preventive possibilities.
MATERIAL AND METHODS

This study was initiated by a Nordic Study Group of ophthalmologists (NORDSYN Study Group) in 1988. A plan was made for investigating the available data on children in the Nordic registers of visual impairment. The basic aim was to start investigations into childhood visual impairment in the Nordic countries. The children with visual impairment born from 1972 through 1989 were included in the Nordic project carried out from 1988 to 1992 (studies I–IV). The coordinator of the project was Ruth Riise from Norway and the group members were Mette Warburg and Thomas Rosenberg from Denmark, Gudmundur Viggosson from Iceland, Egill Hansen and Tor Flage from Norway, and Sirkka-Liisa Rudanko from Finland. The Swedish register of visual impairment was established in 1965, but it had been dormant for a period until re-established in 1990. Therefore, Swedish data is not included in this study.

The aim of the NORDSYN Study Group was to coordinate the registration routines of visual impairment in the Nordic countries for socio-medical statistics and research. It was assumed that the standard of the social and health care was approximately equal in all Nordic countries and more extensive Nordic material for the analysis of the data on childhood visual impairment was wanted.

The Finnish data were obtained from the Finnish Register of Visual Impairment, which is one of the patient registers kept up by the National Research and Development Centre for Welfare and Health (Stakes) in Finland and maintained at the Finnish Federation of the Visually Impaired.

After the Nordic studies (studies I–IV), I performed additional investigations on the Finnish material for more thorough results (studies V–VI). For that purpose, the data was extensively supplemented with additional information from the patient records in ophthalmological, pediatric and obstetric departments in Finnish hospitals and from several statistical registers of the National Research and Development Centre for Welfare and Health (Stakes). Additional knowledge was also acquired by visiting hospitals and examining patient records there. The ocular diagnoses and other medical data from the doctors responsible for the treatments of the children were used.
Classification and definitions of visual impairment in children

The classifications of visual impairment, diagnoses and etiologies varied in the Nordic countries (Table 1). The International Classification of Impairments, Disabilities, and Handicaps (ICIDH) by the World Health Organization (WHO 1980) was used in Finland (a Finnish national modification), Iceland, and Norway (Table 2). The Danish register used the classification of the International Association for the Prevention of Blindness from 1964 (IAPB).

For the diagnostic classification, ICD-8 was used in Denmark, ICD-9 in Finland and Iceland, and IAPB in Norway. The etiological classification used in Denmark was based on the IAPB classification (International Association for the Prevention of Blindness 1964), modified by splitting into a prenatal, a perinatal, and an infantile-juvenile group. The Finnish register used a national coding system for etiological classification. The Icelandic register did not code etiologies. The Norwegian register used the original IAPB-coding system. Information on additional impairments (motor, cognitive, and auditory) was collected and coded in all registers.
Table 1. Description of the Nordic registers of visual impairment

<table>
<thead>
<tr>
<th></th>
<th>Denmark</th>
<th>Finland</th>
<th>Iceland</th>
<th>Norway</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target group</strong></td>
<td>Children</td>
<td>Whole</td>
<td>Whole</td>
<td>Whole</td>
</tr>
<tr>
<td></td>
<td>population</td>
<td>population</td>
<td>population</td>
<td>population</td>
</tr>
<tr>
<td><strong>Classification of visual impairment</strong></td>
<td>IAPB</td>
<td>Modified WHO</td>
<td>WHO</td>
<td>WHO</td>
</tr>
<tr>
<td><strong>Classification of diagnoses</strong></td>
<td>ICD-8</td>
<td>ICD-9</td>
<td>ICD-9</td>
<td>IAPB</td>
</tr>
<tr>
<td><strong>Classification of etiology</strong></td>
<td>Modified IAPB</td>
<td>National</td>
<td>None</td>
<td>IAPB</td>
</tr>
<tr>
<td><strong>Information on additional impairments</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 2. Categories of visual impairment in the International Classification of Diseases, World Health Organization 1973*

<table>
<thead>
<tr>
<th>WHO category of visual impairment</th>
<th>Visual acuity</th>
<th>Visual field diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO 1 Moderate VI</td>
<td>&lt;6/18–6/60</td>
<td></td>
</tr>
<tr>
<td>WHO 2 Severe VI</td>
<td>&lt;6/60–3/60</td>
<td></td>
</tr>
<tr>
<td>WHO 3 Profound VI</td>
<td>&lt;3/60–1/60</td>
<td>&lt;20 degrees, ≥10 degrees</td>
</tr>
<tr>
<td>WHO 4 Near-total blindness</td>
<td>&lt;1/60–light perception</td>
<td>0 degrees</td>
</tr>
<tr>
<td>WHO 5 Total blindness</td>
<td>No light perception</td>
<td>Unknown</td>
</tr>
<tr>
<td>WHO 9 Unknown degree of blindness</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Low vision WHO categories 1-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blindness WHO categories 3-5, 9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Nordic database on visual impairment in children*

The classification of visual impairment according to the definitions by the World Health Organization in the International Classification of Diseases was selected for the Nordic studies (Table 2). The main inclusion criterion was the best corrected visual acuity (BCVA) of less than 6/18 (<0.3) or a visual field diameter of less than 20 degrees. Children with an unspecified degree of residual vision were placed in WHO category 9 and classified as blind (i.e. they belonged into the group of functionally blind children).

It was not possible to convert the Danish data from IAPB to WHO categories and, for comparable figures, the Danish material was re-calculated. Therefore, the Danish study population declined from 1377 to 1158.
The diagnoses and the etiologies of visual impairment and the multiple handicaps were coded according to the system defined by the NORDSYN Study Group (Riise et al 1992). The ophthalmological diagnoses and other medical disorders were based on the original findings in the hospital records. The joint NORDSYN classification demanded a reclassification of all registered cases.

**Classification of diagnoses**

Ophthalmological diagnoses were classified according to the Californian version of ICD-9 (International Classification of Diseases, 9th revision) and the Californian standard nomenclature published by the Californian Association of Ophthalmology, which had been used in Finland since 1983.

**The primary ocular disease**

Due to statistical reasons, only one main ocular diagnosis was registered in the study, although several diseases may have influenced the development of visual impairment. The diagnosis of the last affected eye was registered.

**Cerebral visual impairment**

The diagnosis of cerebral visual impairment was used for the cerebral lesions affecting posterior visual pathways and/or cortical areas, in which cases the ocular pathology did not explain visual impairment.

**Systemic diagnosis**

Systemic diagnoses were coded in accordance with ICD-9. It was necessary to recode the Danish and Norwegian diagnoses. Systemic diagnoses were used when ocular disorders were part of systemic diseases or when an ocular lesion was secondary to a process elsewhere in the body.

**Coding of additional impairment**

A uniform coding system for additional impairments was agreed upon. Additional impairments were registered in the cases of mental, motor, and auditory impairment. A three-digit coding system (mental 100, motor 010, auditory 001) was used for the registration.

**Classification of etiologies**

An etiological standard classification for visual impairment in children was created. The joint NORDSYN classification demanded a reclassification of all registered cases. Supplementary information on possible familial occurrences, parental consanguinity, dysmorphologies or dysfunctions outside the visual system, or special medical histories (birth complications etc.) were used for the etiological classification. When visual impairment was a consequence of a primary disease process involving organ systems other than the visual one, the etiology of the primary disease was used for coding.
Thus, e.g. the etiology of optic nerve atrophy due to neurofibromatosis was genetic. A serological verification in mothers and children was demanded for a specific fetomaternal infectious etiology.

In the joint NORDSYN coding system, the etiology describing the basic biological process or event responsible for the primary ocular disease was selected. The etiology of the last affected eye was selected. Etiological factors were classified under 4 main categories related to the time of the damage: prenatal, perinatal (birth and first 28 days of life), infantile-juvenile (after first 28 days of life), and unknown (time and cause).

Study population

The present study comprises two parts, i.e. the Nordic series (studies I–IV) and the Finnish series (studies V–VI). The Nordic part was performed during the NORDSYN project, which was a retrospective epidemiological cohort study, based on four national registers in the Nordic countries. The total study population of the children with visual impairment in the Nordic series was 2308 (Denmark 1158, Finland 553, Iceland 58, Norway 539). The total study population of the children (<18 years) was 3,303,698. All recorded cases with a visual impairment of BCVA < 0.3 alive on January 1st, 1990 in Denmark, Finland, Iceland, and Norway were included in the Nordic part of the study.

The Finnish part of the study (studies V–VI) was performed after the Nordic series. It comprised 556 recorded children with visual impairment (0–17 years) alive on January 1st, 1990 in Finland. The results of this review are based on the analysis of these 556 Finnish persons.

Methods

The material was compiled from four Nordic national registers of visual impairment (Danish, Finnish, Icelandic, and Norwegian). During many workshops, the NORDSYN Study Group agreed on common classifications and uniformed definitions for the data coding. The different classification systems used by the national registers were made comparable for obtaining a uniform handling and standardized data for a Nordic database.

Each record included the following information: sex, year of birth, year of registration, category of visual impairment, ocular diagnosis, systemic diagnosis, etiology, and additional impairment (mental, mobility, auditory).

The main outcome measures of the study were visual acuity, ophthalmological diagnosis, associated systemic disease, multiple handicap,
gestational age, birth weight, 5-minute Apgar score, and prenatal, perinatal, or infantile-juvenile disorder.


For studies V–VI, the register data was supplemented with the hospital records of the visually impaired children and their mothers and from several registers by the National Research and Development Centre for Welfare and Health (Stakes) in Finland, e.g. from the Medical Birth Register, the Register on Congenital Malformations, the Hospital Discharge Register, and the Finnish Cancer Registry. The permission for the use of the registers and hospital records for scientific purposes was received from the Ministry of Social Affairs and Health.

The other sources supplied data on:

a) **prenatal period**

Maternal age, medical examinations (e.g. ultrasonography, x-rays, magnetic resonance imaging, amnioscopy, fetoscopy, amniocentesis, amniotic fluid analysis), maternal diseases, medications, operations, traumas, use of alcohol, tobacco and drugs, prenatal disorders (i.e. maternal arterial hypertension, pre-eclampsia, infections, uterine hemorrhages, placental disorders, fetal asphyxia), multifetal pregnancies, and unusual status of fetal presentation or birth canal.

b) **perinatal period and children’s later health**

Modes of delivery, infant’s gestational age (GA) and birth weight (BW), perinatal disorders (i.e. asphyxia, respiratory, metabolic, infectious, digestive or blood disorders, brain hemorrhages, hyperbilirubinemia), mechanical ventilation, blood exchange, operations for hydrocephalus, cerebral tumors, congenital malformations, additional impairments, ophthalmic operations for cataract, glaucoma, retinal detachment or other diseases, and retinal cryo therapy.

**Definitions associated with pregnancy, childbirth and infants**

*Prenatal period:* prenatal period was defined as the time from conception to the beginning of the labor.

*Perinatal period:* perinatal period was counted from the beginning of the labor to the 28th day of life.

*Infantile-juvenile period:* Infantile-juvenile period covered the period from 1 month to 18 years of life.
**Pre-eclampsia**: systemic blood pressure >140/90 and proteinuria >0.5 g/day during pregnancy.

**Asphyxia**
The criterion for birth asphyxia was a 5-minute Apgar score of 0–6. Nowadays, pH values in umbilical arteries are used as the criterion for asphyxia (pH <7.16–7.2, severe asphyxia pH <7.0), but pH values were not measured during the 1970–1980s.

**Prematurity**
During the 1970–1980s (until 1987) the classification of prematurity was based on the birth weight (<2500g). Since 1987 the classification is based on the gestational age (<37 weeks). Children born after 41 gestational weeks were over-term.

<table>
<thead>
<tr>
<th>Maturity of infants</th>
<th>Gestational age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over-term</td>
<td>&gt;41 GWs</td>
</tr>
<tr>
<td>Full-term</td>
<td>37–41 GWs</td>
</tr>
<tr>
<td>Preterm</td>
<td>&lt;37 GWs</td>
</tr>
<tr>
<td>Very preterm</td>
<td>&lt;32 GWs</td>
</tr>
<tr>
<td>Extremely preterm</td>
<td>&lt;28 GWs</td>
</tr>
</tbody>
</table>

**Category of birth weight**
- Normal birth weight ≥2500g
- Low birth weight <2500g
- Very low birth weight <1500g
- Extremely low birth weight <1000g

**Mortality**
Mortality rates have been expressed as the number of deaths per 1000 births, or as the percentage of deaths per all births during determined periods.

**Data analysis and statistical methods**
The data was transferred into a computer database using D-base III + software and an IBM PC compatible computer (Studies I–IV). A SAS for Windows 6.12 program (SAS Institute Inc., Espoo, Finland) was used for data processing in the studies V–VI in the Finnish Register of Visual Impairment.

Significant variables for risk factor determinations in visual impairment were defined by Mantel-Haenszel-Chi-Square Test, Mann-Whitney’s U Test, and Fisher’s Exact Test. The independent variables for independent associating factors in visual impairment were analyzed further by stepwise
logistic regression analyses. Comparative statistical analyses of the preterm and full-term children were performed in study V. In addition, Finnish perinatal and vital statistics and obstetric/perinatal literature were used for comparative statistical evaluations. The Finnish National Statistics were used in the assessments of the prevalences and the sex distribution in children with visual impairment.
RESULTS

Study population (I–VI)

The study population consisted of 556 children aged 0–17 with registered visual impairment by January 1st, 1990. Data on their mothers at the time of the corresponding pregnancies and births were also analyzed.

Mothers

Maternal age

Maternal age of the 556 mothers varied from 16 to 44 years (median 27 years).

The proportion of mothers at the typical fertile age of 20–34 (N=464) was 83% in total, 84% of full-term births (N=362) and 82% of preterm births (N=102). In the Finnish population in general, the proportion of pregnant women at the age of 20–34 is the same (82%).

The proportion of younger mothers (<20) (N=28) was 5% in total, 5% (N=20) of full-term births and 6% (N=8) of preterm births. These numbers were somewhat higher than in the general population (3%).

The proportion of older mothers (≥35) (N=64) was 12% in total, 11% (N=49) of full-term births and 12% (N=15) of preterm births. These numbers were lower than in the general population (16%).

The children of the older mothers did not differ essentially from the entire study group: mean GA 37 weeks vs. 38 weeks, blind children 51% vs. 47%, multihandicapped children 46% vs. 50%, malformations in 48% vs. 51%, genetic etiology of visual impairment in 43% vs. 42%, and prenatal unspecified etiology in 23% vs. 22%.

Maternal health and life habits

Maternal chronic diseases were rare, e.g. 10 had diabetes (0.02%). A few serious diseases had developed during the pregnancies, and operations for uteral myoma (N=1), ovarian tumor (N=2), appendicitis (N=2), thyroid gland dysfunction (N=1), colon obstruction (N=1), and renal stones (N=1) had been performed.
Medications had been recorded in 44 pregnant women (8%). The most common medicines were antibiotics, antihypertensives, diuretics, and sedatives. Because of the relatively solitary cases of medications, no etiologic associations were discovered between the use of medicines and visual impairment in the children.

Smoking (N=22) and use of alcohol (N=6) were rarely announced.

Children

*Gender distribution of children with visual impairment*

Of the 556 children, 343 (62%) were males and 213 (38%) females. The male/female ratio was 1.61, which was significantly higher than in the Finnish population in general (1.05; P<0.05). The male excess was also significant in blind children (1.31; P<0.002). Likewise, males were more common both in children born at full term (1.68) and born prematurely (1.44), and in children with isolated visual impairment (1.80) and with additional impairment (1.44). The male dominance was significant for genetic etiology (2.42; P<0.001) and for non-genetic etiology (1.38; P=0.01). In relation to single ophthalmic diagnoses, males were also preponderant in the group of non-genetic optic nerve atrophy (P=0.01).

*Gestational age distribution*

The gestational age (GA) of the children varied from 20 weeks to 45 weeks (median 38 weeks). Of the children 431 (77%) were born at full term and 125 (23%) were born prematurely. The GA in the preterms varied from 20 weeks to 36 weeks (median 30 weeks). Of them, 59 (47%) had been born at GA 20–29 weeks and 66 (53%) at GA 30–36 weeks.

*Birth weight distribution*

The birth weight (BW) of the children varied from 570g to 4730g (median 3080g). In the prematurely born children (N=125), the BW ranged from 570g to 3820g (median 1360g). The proportion of VLBW children (BW <1500g) was 68 (54%), including 37 children with BW 1000g to <1500g (29% of all preterms) and 31 children with BW <1000g (25% of all preterms).

*Prenatal disorders*

Prenatal disorders had been diagnosed in 244 pregnancies (44%), including systemic infections in 102 women (18%), uterine hemorrhages in 41 women (7%), and pre-eclampsia in 36 women (6%). The most common microbes during pregnancy were rubella (9), toxoplasma (5), and other viruses. Venereal infections had not been recorded.

Prenatal disorders were significantly more common in premature
children than in children born at full term (Table 3). They had been recorded in 89/125 women with preterm delivery (71%) and in 155/431 women with full-term delivery (36%).

In 25 women, prenatal disorders had already been recorded during the first trimester of pregnancy. In those cases, the most common disorders had been uterine hemorrhages (N=13) and urinary infections (N=5). A third of the pregnancies with disorders during the first trimester had resulted in preterm births.

**Perinatal disorders**

One or more perinatal disorders were recorded in 252 cases (45%), including respiratory disorders (126 children), birth asphyxia (69 children), infections (61 cases, due e.g. to adenovirus, candida, cytomegalovirus, herpes simplex, rubella, toxoplasma, streptococcus, and staphylococcus), hyperbilirubinemia (49 children), cerebral hemorrhages (41 children), neonatal metabolic and endocrinologic disorders (61 children), constitutional and other complications (60 children), need of mechanical ventilation of 1–12 days (70 children), blood disease (37 children), and blood transfusion (24 children). Severe ocular infections were identified in only 14 cases (rubella 9, toxoplasma 5).

Perinatal disorders were significantly more common in prematurely born children than in children born at full term (Table 3).
Table 3. Differences in the prevalence of prenatal and perinatal disorders between preterm and full-term children with visual impairment (N=556)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preterm (N=125)</th>
<th>Full-term (N=431)</th>
<th>Difference between preterm and full-term children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %</td>
<td>N %</td>
<td>P value (Mantel-Haenszel)</td>
</tr>
<tr>
<td>Pregnancies with prenatal disorders (N=244; 44%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cases</td>
<td>89 71</td>
<td>155 36</td>
<td>0.001</td>
</tr>
<tr>
<td>Maternal infections</td>
<td>36 27</td>
<td>52 12</td>
<td>0.001</td>
</tr>
<tr>
<td>Uterine hemorrhages</td>
<td>25 20</td>
<td>26 6</td>
<td>0.004</td>
</tr>
<tr>
<td>Placental disorders</td>
<td>16 13</td>
<td>17 4</td>
<td>0.003</td>
</tr>
<tr>
<td>Multifetal pregnancies</td>
<td>11 9</td>
<td>13 3</td>
<td>0.008</td>
</tr>
<tr>
<td>Children with perinatal disorders (N=252; 45%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cases</td>
<td>111 89</td>
<td>141 33</td>
<td>0.001</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>92 74</td>
<td>39 9</td>
<td>0.001</td>
</tr>
<tr>
<td>Asphyxia at birth</td>
<td>63 50</td>
<td>7 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infections</td>
<td>33 26</td>
<td>32 7</td>
<td>0.001</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>33 26</td>
<td>16 4</td>
<td>0.001</td>
</tr>
<tr>
<td>Cerebral hemorrhages</td>
<td>28 22</td>
<td>13 3</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>13 10</td>
<td>13 3</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**Asphyxia**

The rate of recorded birth asphyxia, determined by a 5-minute Apgar score of 0–6, was 50% in the preterm group and 2% in the full-term (Table 3). In preterm children, birth asphyxia associated most commonly with cerebral visual impairment and ROP (Table 4). The cases of prenatal asphyxia could not be detected by the antenatal records available.
Table 4. Association of birth asphyxia and the profile of visual impairment in preterm children (N=125)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All preterm children (N=125)</th>
<th>Birth asphyxia (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>All diagnoses of visual impairment</td>
<td>125</td>
<td>63</td>
</tr>
<tr>
<td>ROP</td>
<td>57</td>
<td>34</td>
</tr>
<tr>
<td>Optic nerve atrophy</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>Cerebral visual impairment</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Congenital cataract</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Multiple impairment</td>
<td>83</td>
<td>39</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>Blindness (WHO3–5, 9)</td>
<td>87</td>
<td>49</td>
</tr>
</tbody>
</table>

Fetus presentation and mode of delivery

The rarer types of fetal presentation (e.g. breech presentation) and uterine defects were uncommon. No significant association was found between the visual outcome of the children and the fetal presentation or the mode of delivery (i.e. vaginal delivery, forceps delivery, vacuum extraction, cesarean section).

Diagnoses of visual impairment in children (III, V, VI)

The main ophthalmological groups of visual impairment were retinal diseases (35%), neuro-ophthalmological diseases (29%), and congenital ocular malformations (29%) (Table 5).

In relation to ophthalmological diagnoses, the children born prematurely differed in several respects from those children born at full term.

In preterm children, retinal diseases were prevailing (48%) due to a high prevalence of ROP (46%), also neuro-ophthalmological visual impairment was more common (39%) than in the full-terms (26%). In children born at full term, ocular malformations were most dominating (34%) and more common than in preterm children (12%), whereas the prevalences of retinal diseases (31%) and neuro-ophthalmological diseases (26%) were lower than in preterm children.
Table 5. Main ophthalmic groups of visual impairment in preterm and full-term children

<table>
<thead>
<tr>
<th>Ophthalmic group</th>
<th>All children (N=556)</th>
<th>Preterm children (N=125)</th>
<th>Full-term children (N=431)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Retinal diseases</td>
<td>192</td>
<td>35</td>
<td>60</td>
</tr>
<tr>
<td>Neuro-ophthalmological disorders</td>
<td>164</td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td>Ocular malformations</td>
<td>163</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>Others</td>
<td>37</td>
<td>7</td>
<td>-</td>
</tr>
</tbody>
</table>

**Diagnoses of visual impairment in all children**

Optic nerve atrophy was the leading diagnosis of visual impairment and blindness, followed by retinal dystrophies (Figure 1, Table 6). Of the single diagnoses, congenital cataract was also common in full term children, while ROP was the chief diagnosis of the most immature infants (mean BW 935g). A male dominance was seen in most diagnostic groups, both in preterm and full-term children, except in cases with cerebral visual impairment, Lebers’ amaurosis, and tapetoretinal dystrophy (Table 7). The infants born after 32 gestational weeks were not afflicted by ROP (Table 8).
Table 6. The main diagnoses of visual impairment in preterm and full-term children

<table>
<thead>
<tr>
<th>Diagnosis of visual impairment</th>
<th>All children (N=556)</th>
<th>Preterm children (N=125)</th>
<th>Full-term children (N=431)</th>
<th>Difference between preterm and full-term children</th>
<th>P value (Mantel-Haenszel)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Optic nerve atrophy</td>
<td>120</td>
<td>22</td>
<td>35</td>
<td>28</td>
<td>85</td>
</tr>
<tr>
<td>Inherited retinal dystrophy</td>
<td>111</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>111</td>
</tr>
<tr>
<td>Neuronal ceroid lipofuscinosis</td>
<td>30</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>X-linked retinoschisis</td>
<td>27</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>Leber's congenital amaurosis</td>
<td>24</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>24</td>
</tr>
<tr>
<td>Tapetoretinal dystrophy</td>
<td>19</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>19</td>
</tr>
<tr>
<td>Other retinal dystrophy</td>
<td>11</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>Congenital cataract</td>
<td>59</td>
<td>11</td>
<td>5</td>
<td>4</td>
<td>54</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>57</td>
<td>10</td>
<td>57</td>
<td>46</td>
<td>-</td>
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<tr>
<td>Cerebral visual impairment</td>
<td>44</td>
<td>8</td>
<td>15</td>
<td>12</td>
<td>29</td>
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<tr>
<td>Choroidal coloboma</td>
<td>25</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>Optic nerve hypoplasia</td>
<td>19</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Aniridia</td>
<td>18</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Albinism</td>
<td>17</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>17</td>
</tr>
<tr>
<td>Congenital nystagmus</td>
<td>16</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Achromatopsia</td>
<td>13</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>High myopia</td>
<td>11</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>Optic disc anomaly</td>
<td>11</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>8</td>
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<tr>
<td>Iridocyclitis</td>
<td>5</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>5</td>
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<tr>
<td>Microphthalmus</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Others</td>
<td>22</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>All</td>
<td>556</td>
<td>100</td>
<td>125</td>
<td>100</td>
<td>431</td>
</tr>
</tbody>
</table>
Figure 1. Distribution of diagnoses of visual impairment in all children (N=556)

Table 7. The main diagnoses of visual impairment in preterm and full-term children by gender (N=556)

<table>
<thead>
<tr>
<th>Diagnosis of visual impairment</th>
<th>All children M/F ratio</th>
<th>Preterm children M/F ratio</th>
<th>Full-term children M/F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic nerve atrophy</td>
<td>1.73</td>
<td>2.18</td>
<td>1.58</td>
</tr>
<tr>
<td>Congenital cataract</td>
<td>1.68</td>
<td>1.50</td>
<td>1.70</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>1.11</td>
<td>1.11</td>
<td>-</td>
</tr>
<tr>
<td>Cerebral visual impairment</td>
<td>0.61</td>
<td>1.14</td>
<td>0.38</td>
</tr>
<tr>
<td>Neuronal ceroid lipofuscinosis</td>
<td>2.33</td>
<td>-</td>
<td>2.33</td>
</tr>
<tr>
<td>X-linked retinoschisis</td>
<td>26.00</td>
<td>-</td>
<td>26.00</td>
</tr>
<tr>
<td>Choroidal coloboma</td>
<td>2.13</td>
<td>-</td>
<td>2.13</td>
</tr>
<tr>
<td>Leber’s amaurosis</td>
<td>0.71</td>
<td>-</td>
<td>0.71</td>
</tr>
<tr>
<td>Optic nerve hypoplasia</td>
<td>2.17</td>
<td>1.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Tapetoretinal dystrophy</td>
<td>0.56</td>
<td>-</td>
<td>0.56</td>
</tr>
<tr>
<td>Aniridia</td>
<td>0.80</td>
<td>-</td>
<td>1.0</td>
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<tr>
<td>Albinism</td>
<td>4.67</td>
<td>-</td>
<td>4.67</td>
</tr>
<tr>
<td>Total</td>
<td>1.61</td>
<td>1.44</td>
<td>1.68</td>
</tr>
</tbody>
</table>
Table 8. The main diagnosis of visual impairment in preterm children by gestational age (N=125)

<table>
<thead>
<tr>
<th>Diagnosis of visual impairment</th>
<th>All preterm children</th>
<th>&lt;26 GWs</th>
<th>26–27 GWs</th>
<th>28–29 GWs</th>
<th>30–32 GWs</th>
<th>33–36 GWs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>57</td>
<td>16</td>
<td>28</td>
<td>15</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>35</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Cerebral visual impairment</td>
<td>15</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Congenital cataract</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
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<tr>
<td>Other diagnoses</td>
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<td>-</td>
<td>-</td>
<td>1</td>
<td>8</td>
<td>1</td>
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<tr>
<td>All diagnoses</td>
<td>125</td>
<td>16</td>
<td>13</td>
<td>18</td>
<td>14</td>
<td>25</td>
</tr>
</tbody>
</table>

Diagnoses of visual impairment in blind children

The proportion of blind children (WHO categories 3–5, 9) was 256 (46%), and 57 children (10%) were totally blind (WHO 5) (Table 9). The most common single diagnoses in blind children were optic nerve atrophy (N=60), ROP (N=47), cerebral visual impairment (N=33), and Leber’s congenital amaurosis (N=19), which represented 62% of all blinding diseases (i.e. 24%, 18%, 13%, and 7%) (Figure 2a, Figure 2b). Cerebral visual impairment predominated in the blind children born at full term, while cerebral visual impairment and ROP were equally prevailing in the prematurely born children.

In the 57 totally blind children, ROP was the most predominating disease (N=20) (Table 9). The totally blind children born at full term (N=33) were affected mainly by optic nerve atrophy (N=9), Leber’s congenital amaurosis (N=9), and cerebral visual impairment (N=5). Whereas the prematurely born blind children (N=24) were impaired mostly by ROP (N=20).
Table 9. The main diagnosis of visual impairment in blind children (N=256)

<table>
<thead>
<tr>
<th>Diagnosis of visual impairment</th>
<th>All children (N=556)</th>
<th>Blind children (N=256)</th>
<th>Totally blind children (N=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Optic nerve atrophy</td>
<td>120</td>
<td>22</td>
<td>60</td>
</tr>
<tr>
<td>Inherited retinal dystrophy</td>
<td>111</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td>Neuronal ceroid lipofuscinosis</td>
<td>30</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>X-linked retinoschisis</td>
<td>27</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Leber’s congenital amaurosis</td>
<td>24</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Tapetoretinal dystrophy</td>
<td>19</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Other retinal dystrophy</td>
<td>11</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Congenital cataract</td>
<td>59</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>57</td>
<td>10</td>
<td>47</td>
</tr>
<tr>
<td>Cerebral visual impairment</td>
<td>44</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>Choroidal coloboma</td>
<td>25</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Optic nerve hypoplasia</td>
<td>19</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Aniridia</td>
<td>18</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Others</td>
<td>103*</td>
<td>18</td>
<td>31**</td>
</tr>
<tr>
<td>All</td>
<td>556</td>
<td>100</td>
<td>256</td>
</tr>
</tbody>
</table>

* Albinism 17, congenital nystagmus 16, achromatopsia 13, high myopia 11, optic disc anomaly 11, iridocyclitis 5, microphthalmus 4, retinoblastoma 4, others 22.
** Optic disc anomaly 8, achromatopsia 5, microphthalmus 3, retinoblastoma 3, chorioretinitis 2 (including toxoplasmosis 1), persistent hyperplastic primary vitreous 2, albinism 1, congenital glaucoma 1, corneal corrosion 1, corneal dystrophy 1, eye-muscle-brain disease 1, high myopia 1, retinal detachment 1, retinal degeneration (other) 1.
Figure 2a. Distribution of diagnoses of visual impairment in blind children (N=256)

Figure 2b. Prevalence of diagnoses of visual impairment in all (N=556) and blind (N=256) children
Multiple impairment in children with visual impairment (I–VI)

**Congenital malformations**

The number of children with congenital malformations was 288 (52%) (Table 10). Ocular malformations were found in 186 children (33%), including congenital cataract in 59, chorioretinal coloboma in 25, optic nerve hypoplasia in 19, aniridia in 18, specified anomalies of optic disc in 11, and other malformations in 54 children. Ocular malformations were less frequent in the preterm infants (18%) than in the full-terms (38%) (P=0.001). In the full-term children, ocular malformations were the primary cause of visual impairment in 148/431 (34%).

All congenital malformations were significantly less common in the prematurely born children (26%) than in the full-terms (50%) (P=0.001). Non-ocular malformations were recorded in 172 children (31%), and both ocular and non-ocular malformations existed in 70 (13%). The rates of non-ocular malformations were equal in the preterm (38; 30%) and the full-term children (134; 31%).

Hydrocephalus had been diagnosed in 20 preterm children and in 22 full-term children. They have not been included in the malformation group, however, due to difficulties at distinguishing the congenital cases of hydrocephalus from the secondary posthemorrhagic ones on the basis of the patient histories.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All children (N=556)</th>
<th>Preterm children (N=125)</th>
<th>Full-term children (N=431)</th>
<th>Difference between preterm and full-term children</th>
<th>P value (Mantel-Haenszel)</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular malformations</td>
<td>186 33</td>
<td>22 18</td>
<td>164 38*</td>
<td></td>
<td>P=0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All congenital malformations</td>
<td>288 52</td>
<td>33 26</td>
<td>213 50</td>
<td></td>
<td>P=0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* In 148 children (34%), an ocular malformation was the primary cause of visual impairment.
Systemic diseases
Systemic diseases were detected in 267 children (48%). The most common systemic disorders were cerebral palsy in 143 (22%) and epilepsy in 128 (20%) (Table 11). Of the preterm children, 89 (64%) had systemic disorders. Of the full-term children, 187 (43%) were affected by one or several systemic diseases. All children with neuronal ceroid lipofuscinosis and albinism, and the majority of children with optic nerve atrophy and cerebral visual impairment had one or several systemic diseases (Table 12).

<table>
<thead>
<tr>
<th>Systemic disease</th>
<th>All children (N=556)</th>
<th>Preterm children (N=125)</th>
<th>Full-term children (N=431)</th>
<th>Difference between preterm and full-term children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>P value (Mantel-Haenszel)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>22</td>
<td>54</td>
<td>18</td>
<td>0.001</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>20</td>
<td>36</td>
<td>19</td>
<td>0.001</td>
</tr>
<tr>
<td>All systemic</td>
<td>48</td>
<td>64</td>
<td>43</td>
<td>0.001</td>
</tr>
<tr>
<td>diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Table 12. The main ophthalmological diagnosis in full-term children with visual impairment and systemic diseases

<table>
<thead>
<tr>
<th>Diagnosis of visual impairment</th>
<th>Full-term children (N=431)</th>
<th>Full-term children with systemic disease (N=187)</th>
<th>% by diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Optic nerve atrophy</td>
<td>85</td>
<td>71</td>
<td>84</td>
</tr>
<tr>
<td>Congenital cataract</td>
<td>54</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Neuronal ceroid lipofuscinosis</td>
<td>30</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>Cerebral visual impairment</td>
<td>29</td>
<td>22</td>
<td>76</td>
</tr>
<tr>
<td>X-linked retinoschisis</td>
<td>27</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Choroidal coloboma</td>
<td>25</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Leber’s congenital amaurosis</td>
<td>24</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Tapetoretinal dystrophy</td>
<td>19</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Albinism</td>
<td>17</td>
<td>17</td>
<td>100</td>
</tr>
<tr>
<td>Optic nerve hypoplasia</td>
<td>17</td>
<td>9</td>
<td>53</td>
</tr>
<tr>
<td>Aniridia</td>
<td>16</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Others</td>
<td>88*</td>
<td>17</td>
<td>19</td>
</tr>
</tbody>
</table>

*Achromatopsia 13, congenital nystagmus 13, retinal dystrophy (single/unspecifed) 11, high myopia 11, optic disc anomaly 8, congenital glaucoma 7, iridocyclitis 5, chorioretinitis 4 (including toxoplasmosis 2), microphthalmus 4, retinoblastoma 4, persistent hyperplastic primary vitreous 3, corneal corosion 1, corneal dystrophy 1, eye-muscle-brain anomaly 1, retinal detachment 1, retinal degeneration (other) 1.

### Additional impairment

Additional impairment was detected in 276 of the 556 children (50%) including cognitive impairment in 39% and motor impairment in 33% (Table 13). More than one other impairment was present in 26%. The rate of additional impairment was significantly higher in blind children than in children with low vision (P<0.0001). The rate of additional impairment was especially high in children with neuronal ceroid lipofuscinosis (100%), cerebral visual impairment (95%), optic nerve atrophy (78%), and optic nerve hypoplasia (63%) (Table 14; Figure 3). Additional impairment was more common in preterm children (66%) than in full-terms (45%) (P=0.001) (Table 15).
### Table 13. Additional impairment in children with low vision and blindness

<table>
<thead>
<tr>
<th>Additional impairment</th>
<th>All children (N=556)</th>
<th>Children with low vision (N=300)</th>
<th>Blind children (N=256)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>219</td>
<td>39</td>
<td>78</td>
</tr>
<tr>
<td>Motor impairment</td>
<td>183</td>
<td>33</td>
<td>65</td>
</tr>
<tr>
<td>Auditory impairment</td>
<td>34</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Several additional impairments</td>
<td>142</td>
<td>26</td>
<td>42</td>
</tr>
<tr>
<td>All children with additional impairment</td>
<td>276</td>
<td>50</td>
<td>110</td>
</tr>
</tbody>
</table>

### Table 14. The main ophthalmological diagnosis in children with visual and additional impairment

<table>
<thead>
<tr>
<th>Diagnosis of visual impairment</th>
<th>All children (N=556)</th>
<th>Children with additional impairment (N=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Optic nerve atrophy</td>
<td>120</td>
<td>94</td>
</tr>
<tr>
<td>Congenital cataract</td>
<td>59</td>
<td>19</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>57</td>
<td>26</td>
</tr>
<tr>
<td>Cerebral visual impairment</td>
<td>44</td>
<td>29</td>
</tr>
<tr>
<td>Neuronal ceroid lipofuscinosis</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>X-linked retinoschisis</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Choroidal coloboma</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Leber's congenital amaurosis</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Optic nerve hypoplasia</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Tapetoretinal dystrophy</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Aniridia</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>Albinism</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Congenital nystagmus</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Achromatopsia</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>High myopia</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Others*</td>
<td>57</td>
<td>31</td>
</tr>
<tr>
<td>All diagnoses</td>
<td>556</td>
<td>276</td>
</tr>
</tbody>
</table>

* Optic disc anomaly 11, retinal dystrophy (single/unspecified) 11, chorioretinitis 7 (including toxoplasmosis 5), congenital glaucoma 7, iridocyclitis 5, microphthalmus 4, retinoblastoma 4, persistent hyperplastic primary vitreous 3, corneal corrosion 1, corneal dystrophy 1, eye-muscle-brain disease 1, retinal detachment 1, retinal degeneration (other) 1.
Figure 3. Distribution of ophthalmological diagnoses in children with visual and additional impairment (N=276)
Table 15. The main ophthalmological diagnosis in children with visual and additional impairment, born at full-term and prematurely

<table>
<thead>
<tr>
<th>Diagnosis of visual impairment</th>
<th>Full-term children (N=431)</th>
<th>Full-term children with additional impairment (N=193)</th>
<th>Preterm children (N=125)</th>
<th>Preterm children with additional impairment (N=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N%</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>0</td>
<td>0</td>
<td>57</td>
<td>26</td>
</tr>
<tr>
<td>Optic nerve atrophy</td>
<td>85</td>
<td>60</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Congenital cataract</td>
<td>54</td>
<td>16</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Neuronal ceroid lipofuscinosis</td>
<td>30</td>
<td>30</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Cerebral visual impairment</td>
<td>29</td>
<td>14</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>X-linked retinoschisis</td>
<td>27</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Choroidal coloboma</td>
<td>25</td>
<td>10</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Leber’s amaurosis</td>
<td>24</td>
<td>4</td>
<td>17</td>
<td>-</td>
</tr>
<tr>
<td>Tapetoretinal dystrophy</td>
<td>19</td>
<td>5</td>
<td>26</td>
<td>-</td>
</tr>
<tr>
<td>Albinism</td>
<td>17</td>
<td>1</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Optic nerve hypoplasia</td>
<td>17</td>
<td>11</td>
<td>65</td>
<td>2</td>
</tr>
<tr>
<td>Aniridia</td>
<td>16</td>
<td>5</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>88*</td>
<td>37</td>
<td>42</td>
<td>9**</td>
</tr>
<tr>
<td>All diagnoses</td>
<td>431</td>
<td>193</td>
<td>45</td>
<td>125</td>
</tr>
</tbody>
</table>

*Achromatopsia 13, congenital nystagmus 13, retinal dystrophy (single/unspecified) 11, high myopia 11, optic disc anomaly 8, congenital glaucoma 7, iridocyclitis 5, chorioretinitis 4 (including toxoplasmosis 2), microphthalmus 4, retinoblastoma 4, persistent hyperplastic primary vitreous 3, corneal corrosion 1, corneal dystrophy 1, eye-muscle-brain disease 1, retinal detachment 1, retinal degeneration (other) 1.

** Chorioretinitis (toxoplasmosis) 3, congenital nystagmus 3, optic disc anomaly 3.
WHO categories of visual impairment in children (I, V, VI)

In this study, 300 children (54%) had low vision (WHO 1-2) and 256 children (46%) were blind (WHO 3-5,9) (Table 16). Of the blind, 153 children (28%) had been blind since birth and 30 children (5%) had been totally blind since birth.

The blindness rate was higher in boys (58%) than in girls (42%) (Mantel-Haenszel P=0.002), in children with multiple impairments and in preterm children (P=0.001) (Table 16). Among the ELBW children, the proportion of the blind was 90% (Table 17).

<table>
<thead>
<tr>
<th>WHO categories of visual impairment</th>
<th>All children (N=556)</th>
<th>Preterm children (N=125)</th>
<th>Full-term children (N=431)</th>
<th>Solitary visual impairment (N=280)</th>
<th>Cases with additional impairment (N=276)</th>
<th>Cases with congenital malformations (N=288)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>WHO 1</td>
<td>44</td>
<td>25</td>
<td>50</td>
<td>59</td>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>WHO 2</td>
<td>9</td>
<td>5</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>WHO 3</td>
<td>7</td>
<td>9</td>
<td>7</td>
<td>6</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>WHO 4</td>
<td>17</td>
<td>27</td>
<td>14</td>
<td>12</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>WHO 5</td>
<td>10</td>
<td>19</td>
<td>8</td>
<td>9</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>WHO 9</td>
<td>13</td>
<td>15</td>
<td>11</td>
<td>5</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>WHO1–2</td>
<td>54</td>
<td>30</td>
<td>60</td>
<td>68</td>
<td>39</td>
<td>49</td>
</tr>
<tr>
<td>WHO 3–5,9</td>
<td>46</td>
<td>70</td>
<td>40</td>
<td>32</td>
<td>61</td>
<td>51</td>
</tr>
</tbody>
</table>

Table 16. WHO categories of visual impairment by preterm/full-term birth and morbidity
Table 17. WHO categories of visual impairment in preterm children by birth weight

<table>
<thead>
<tr>
<th>WHO categories of visual impairment</th>
<th>All preterm children (N=125; 100%)</th>
<th>Birth weight &lt;1000g (N=31; 25%)</th>
<th>Birth weight 1000g-1499g (N=37; 30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>WHO 1</td>
<td>32</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>WHO 2</td>
<td>6</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>WHO 3</td>
<td>11</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>WHO 4</td>
<td>33</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>WHO 5</td>
<td>24</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>WHO 9</td>
<td>19</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Low Vision (WHO 1–2)</td>
<td>38</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Blind (WHO 3–5, 9)</td>
<td>87</td>
<td>70</td>
<td>28</td>
</tr>
</tbody>
</table>

Etiology of visual impairment in children (II)

The main etiologies of visual impairment in children were genetic (42%), prenatal (30%) and perinatal (21%). The etiology was genetic in 53% of the full-term children and in 5% of the preterm (Table 18). Genetic factors were responsible for 57% of solitary visual impairment and for 27% of multiple impairments (Table 19). The most common inherited diseases were neuronal ceroid lipofuscinosis, x-linked juvenile retinoschisis, Leber’s congenital amaurosis, and congenital cataract (Table 20).

In children with prenatal and perinatal etiology of visual impairment, multiple impairments were more common than solitary visual visual impairment (Table 19). Prenatal infections and smoking during pregnancy had occurred somewhat more frequently in the cases with prenatal unspecified etiology (22% vs. 18% and 10% vs. 4%). Cerebral palsy, epilepsy, and congenital hydrocephalus were also slightly more common in the children with prenatal unspecified etiology (31% vs 22%, 28% vs. 20%, and 18% vs 12%).

Prenatal unspecified factors and prematurity were also prevailing etiologies in children with optic nerve atrophy and congenital malformations (Table 21). One fetal alcohol syndrome case was found. That child was born at 34 GWs with a BW of 2200g, with optic nerve hypoplasia, cognitive impairment, and multiple malformations. In two cases, the pregnancies had been induced by clomiphene and resulted in twin pregnancies, preterm births, and combined cognitive and motor impairments. No children born after an assisted conception were included.
In blind children, the main etiologies of visual impairment were genetic in 91 (35%), perinatal complications in 75 (29%), and prenatal unspecified in 44 (17%). In total blindness, the main etiologies were prematurity in 21 (37%), genetic in 18 (32%), and prenatal unspecified in 9 (16%).

The infantile-juvenile etiologies were relatively rare (6%) and most frequently they associated with non-infectious CNS diseases.

<table>
<thead>
<tr>
<th>Etiology of visual impairment</th>
<th>All children (N=556)</th>
<th>Full-term children (N=431)</th>
<th>Preterm children (N=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% of all children</td>
<td>N</td>
</tr>
<tr>
<td>Genetic (including 13 cases with a cytogenetic chromosomal aberration)</td>
<td>234</td>
<td>42</td>
<td>228</td>
</tr>
<tr>
<td>Prenatal</td>
<td>168</td>
<td>30</td>
<td>148</td>
</tr>
<tr>
<td>Prenatal infectious</td>
<td>26</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Intoxication</td>
<td>2</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Prenatal specified</td>
<td>17</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Prenatal unspecified</td>
<td>123</td>
<td>22</td>
<td>115</td>
</tr>
<tr>
<td>Perinatal</td>
<td>115</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Prematurity</td>
<td>102</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Perinatal complication</td>
<td>13</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Infantile-juvenile</td>
<td>31</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>Infectious, infantile-juvenile</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Trauma</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Non-infectious CNS disease</td>
<td>17</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Other general disease</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Unknown time and cause</td>
<td>8</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>556</td>
<td>100</td>
<td>431</td>
</tr>
</tbody>
</table>
Table 19. Etiology of visual impairment in children with solitary visual impairment and multiple impairment (N=556)

<table>
<thead>
<tr>
<th>Etiology of visual impairment</th>
<th>All children (N=556)</th>
<th>Solitary visual impairment (N=280)</th>
<th>Additional impairment (N=276)</th>
<th>Difference between solitary visual and multiple impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Genetic (including 13 chromosomal defects)</td>
<td>234</td>
<td>42.00</td>
<td>159</td>
<td>57.00</td>
</tr>
<tr>
<td>Prenatal</td>
<td>168</td>
<td>30.11</td>
<td>66</td>
<td>24.29</td>
</tr>
<tr>
<td>Prenatal infectious</td>
<td>26</td>
<td>5.61</td>
<td>6</td>
<td>2.14</td>
</tr>
<tr>
<td>Intoxication</td>
<td>2</td>
<td>0.35</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prenatal specified</td>
<td>17</td>
<td>3.09</td>
<td>3</td>
<td>1.07</td>
</tr>
<tr>
<td>Prenatal unspecified</td>
<td>123</td>
<td>22.19</td>
<td>57</td>
<td>20.64</td>
</tr>
<tr>
<td>Perinatal</td>
<td>115</td>
<td>20.82</td>
<td>35</td>
<td>12.86</td>
</tr>
<tr>
<td>Prematurity</td>
<td>102</td>
<td>18.75</td>
<td>32</td>
<td>11.43</td>
</tr>
<tr>
<td>Perinatal complication</td>
<td>13</td>
<td>2.36</td>
<td>3</td>
<td>1.07</td>
</tr>
<tr>
<td>Infantile-Juvenile</td>
<td>31</td>
<td>5.59</td>
<td>15</td>
<td>5.36</td>
</tr>
<tr>
<td>Infectious, infantile-juvenile</td>
<td>5</td>
<td>0.91</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Trauma</td>
<td>5</td>
<td>0.91</td>
<td>2</td>
<td>0.71</td>
</tr>
<tr>
<td>Non-infectious CNS disease</td>
<td>17</td>
<td>3.09</td>
<td>11</td>
<td>3.93</td>
</tr>
<tr>
<td>Other general disease</td>
<td>4</td>
<td>0.74</td>
<td>2</td>
<td>0.71</td>
</tr>
<tr>
<td>Unknown time and cause</td>
<td>8</td>
<td>1.45</td>
<td>5</td>
<td>1.78</td>
</tr>
</tbody>
</table>
### Table 20. Hereditary ophthalmic causes of visual impairment in children

<table>
<thead>
<tr>
<th>Ophthalmic diagnosis</th>
<th>N</th>
<th>% of all genetic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuronal ceroid lipofuscinosis</td>
<td>30</td>
<td>13</td>
</tr>
<tr>
<td>X-linked juvenile retinoschisis</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>Leber's congenital amaurosis</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Congenital cataract</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Choroidal coloboma</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>Tapetoretinal dystrophy</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Albinism</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Aniridia</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Optic nerve atrophy</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Achromatopsia</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Other retinal dystrophy</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Others</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>234</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 21. Etiology of optic nerve atrophy as the cause of visual impairment

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Optic nerve atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Genetic</td>
<td>16</td>
</tr>
<tr>
<td>Prenatal infectious</td>
<td>5</td>
</tr>
<tr>
<td>Prenatal other specified</td>
<td>6</td>
</tr>
<tr>
<td>Prenatal unspecified</td>
<td>34</td>
</tr>
<tr>
<td>Prematurity</td>
<td>31</td>
</tr>
<tr>
<td>Perinatal complication</td>
<td>5</td>
</tr>
<tr>
<td>Infantile-juvenile /non-infectious CNS disease</td>
<td>14</td>
</tr>
<tr>
<td>Unknown</td>
<td>9</td>
</tr>
<tr>
<td>All</td>
<td>120</td>
</tr>
</tbody>
</table>
Risk factors of visual impairment in children (V, VI)

Prematurity was a very strong risk factor for visual impairment, blindness and additional impairment in children. Both prenatal disorders and perinatal disorders were significant risk factors for visual impairment in preterm children. Prenatal infections, neonatal respiratory disorders, asphyxia, hyperbilirubinemia, and mechanical ventilation for more than 2 weeks were independent risk factors for visual impairment according to the stepwise logistic regression analysis and the Mann-Whitney U test (Table 22). Neonatal hypoglycemia in preterm infants was a nearly significant independent factor in the logistic regression analysis. It had been present in 10% of the preterms and in 4% of the full-terms (Mantel-Haenszel P=0.002).

The lower the gestational age and the birth weight of preterm infants, the higher the risk for visual impairment and blindness in cases with BWs <1500g (P=0.001) and with GAs <30 weeks (P=0.007).

The risk for visual impairment was also significantly higher in male children, both in full-term and preterm cases.

Table 22. Risk factors of visual impairment in preterm infants (N=125)

(Stepwise logistic regression analysis and Mann-Whitney U test)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Probability level</th>
<th>Odds ratio</th>
<th>95% Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>&lt; 0.001</td>
<td>8.96</td>
<td>4.91</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>&lt; 0.001</td>
<td>6.40</td>
<td>2.60</td>
</tr>
<tr>
<td>Asphyxia at birth</td>
<td>&lt; 0.001</td>
<td>3.82</td>
<td>2.10</td>
</tr>
<tr>
<td>Prenatal infections</td>
<td>&lt; 0.050</td>
<td>2.15</td>
<td>1.05</td>
</tr>
<tr>
<td>Duration of mechanical ventilation &gt;2 weeks (Mann-Whitney U)</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prevalence and incidence of visual impairment in children (I, V, VI)

The age-specific prevalence of visual impairment (VI) in Finnish children of 0–17 years and alive on January 1st, 1990 was 49/100,000 (from the Finnish child population of 1,138,326). For children born at full term and prematurely, the corresponding prevalences were 38/100,000 and
11/100,000. The prevalences of visual impairment in children are described in Table 23 by WHO categories, etiologies, general health, and morbidity.

The prevalences of the most common diagnoses of visual impairment in children were 11/100,000 for optic nerve atrophy, 5/100,000 for congenital cataract, 5/100,000 for ROP, and 4/100,000 for cerebral visual impairment. The prevalences of VI in the most common inherited retinal diseases were 3/100,000 for neuronal ceroid lipofuscinosis and 2/100,000 for x-linked juvenile retinoschisis, Leber’s congenital amaurosis and tapetoretinal dystrophies. The prevalence was also 2/100,000 for choroidal coloboma, optic nerve hypoplasia, aniridia, and ocular albinism.

The incidence of visual impairment per 1000 births during the 18 years from 1972 through 1989 was 0.5 /1000 for all children, 0.3 /1000 for full-term children, and 2.2 /1000 for preterm children, according to the vital statistics of the Statistical Yearbook of Finland 1998 and the Finnish perinatal statistics 1987–2000 by the National Research and Development Centre for Welfare and Health (Stakes) (i.e. 1,138,284 child births, including 1,081,370 full term births and 56,914 preterm births).

During the study period, the proportion of registered blind children increased from 95/298 (32%) in the 1970s to 161/258 (62%) in the 1980s, and the proportion of children with ROP rose from 21/298 (7%) in the 1970s to 36/258 (14%) by 1989.
### Table 23. Age-specific prevalence of visual impairment /100,000 Finnish children aged 0–17 in 1989 (N=1,138,326)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of children</th>
<th>Prevalence of visual impairment /100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHO category of visual impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All categories</td>
<td>556</td>
<td>49</td>
</tr>
<tr>
<td>Low vision (WHO 1–2)</td>
<td>300</td>
<td>26</td>
</tr>
<tr>
<td>Blindness (WHO 3–5,9)</td>
<td>256</td>
<td>23</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic</td>
<td>234</td>
<td>21</td>
</tr>
<tr>
<td>Prenatal</td>
<td>168</td>
<td>15</td>
</tr>
<tr>
<td>Perinatal</td>
<td>115</td>
<td>10</td>
</tr>
<tr>
<td>Other etiology</td>
<td>39</td>
<td>3</td>
</tr>
<tr>
<td><strong>General health</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solitary visual impairment</td>
<td>280</td>
<td>25</td>
</tr>
<tr>
<td>Additional impairment</td>
<td>276</td>
<td>24</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>219</td>
<td>19</td>
</tr>
<tr>
<td>Motor impairment</td>
<td>183</td>
<td>16</td>
</tr>
<tr>
<td>Multi-impairment</td>
<td>142</td>
<td>13</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>267</td>
<td>24</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>146</td>
<td>13</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>127</td>
<td>11</td>
</tr>
<tr>
<td>Congenital malformation</td>
<td>288</td>
<td>25</td>
</tr>
<tr>
<td>Ocular malformations</td>
<td>186</td>
<td>16</td>
</tr>
<tr>
<td>Non-ocular malformations</td>
<td>172</td>
<td>15</td>
</tr>
</tbody>
</table>

### Mortality of children with visual impairment (V, VI)

The mortality rate of children (N=62) during 1972–1989 was 11%, in full-term children (N=57) 13%, and in preterm children (N=5) 4%. The mortality was significantly higher than in the Finnish child population in general (0.4%), and equal for both genders.
This is the first examination of childhood visual impairment in the whole child population throughout Finland. The main aim was to investigate the prevalence and causes of childhood visual impairment in the Nordic countries and Finland, with special attention to risk factors and further prevention of visual impairment in children. Another aim was to create an uniform classification and coding system for visual impairment in children for statistics and research. Data on children with visual impairment born from 1972 through 1989 were obtained from the national registers of visual impairment in Denmark, Finland, Iceland, and Norway.

The number of registered children with visual impairment aged 0–17 was 556 in Finland by January 1st, 1990. The age-specific prevalences of visual impairment in 1989 in the four Nordic countries were 105/100,000 in Denmark, 49/100,000 in Finland, 76/100,000 in Iceland and 55/100,000 in Norway. Most probably, variations in the registration activity influenced the difference in the Nordic prevalences, e.g. on the higher numbers of children with cognitive impairment in Denmark. Some underregistration, especially in cases with multiple handicaps, has been obvious in Finland.

The proportion of preterm children with visual impairment was higher than suggested, i.e. nearly one fourth of the total Finnish material (N=125; 23%). Preterm birth was the major risk for visual impairment in Finnish children. The relative proportion of children with retinopathy of prematurity and blind children even increased from the 1970s through the 1980s in Finland. Also the incidence of neuro-ophthalmological impairment was high and increasing from the 1970s through the 1980s due to the higher survival of very low birth weight infants. Our findings are linear with the pediatric studies by Olsen et al (1997), who found periventricular leukomalacia, with risks of cerebral visual impairment in 32% of the children born between 1985–1986 with a birth weight of <1750g in the northern Finland.

We found that the visual prognosis correlated directly with the length of the fetal gestational period, and the prognosis was clearly better in the children having reached a gestational age of ≥33 weeks. Of the visually impaired preterm children born at a gestational age of <33 weeks, 78% were blind. The blindness rate was 81% in the very low birth weight infants and 90% in the extremely low birth weight infants.

The maternal age distribution was equal to that of the Finnish pregnant population in general. According to hospital records, the mean health of the mothers had been excellent prior to the pregnancy. Systemic diseases
and need for medications had been rare. In comparison with pregnancies and births in general, however, significantly higher numbers of prenatal and perinatal disorders had been recorded in our cases. Infections during pregnancy were associated with preterm birth and visual impairment. Thus, it is obvious that the health problems of pregnant women need to be noted and treated carefully.

Profile of children with visual impairment

Severity of visual impairment
The majority of blindness was caused by neuro-ophthalmological disorders (37%), retinopathy of prematurity (18%), and inherited retinal dystrophies (16%). A considerable portion of the children had been blind since birth (28%). Additional impairments, systemic diseases and malformations occurred more commonly in the blind children than in the children with low vision. In the prematurely born children the conditions also occurred more frequently than in the full-terms.

Of the preterm children, 54% were born with a birth weight <1500g and 25% <1000g. In the cases with retinopathy of prematurity, cerebral visual impairment, and optic nerve atrophy, the median birth weights were 930g, 1830g and 1850g. A significant correlation was seen between low birth weight and blindness (P=0.001). Retinopathy of prematurity was the visual impairment diagnosis in every child with a birth weight <1000g, and 90% of them were blind.

For advancing the prevention of childhood blindness, additional improvements are required to prevent very preterm deliveries and to protect fetuses and infants from brain damage. Various inherited retinal dystrophies in children, with no real cure presently, will also require intense work for years ahead.

Diagnoses of visual impairment
Optic nerve atrophy was the leading cause of visual impairment and blindness in children, 35% of the blind in the Nordic series and 24% in the Finnish. In the majority of cases (around 90%), the etiology of optic nerve atrophy was non-genetic, both in the Nordic and Finnish series. In the Finnish series, the prevalences of the main single diagnoses of visual impairment were 11/100,000 for optic nerve atrophy, 5/100,000 for congenital cataract and for ROP, 4/100,000 for cerebral visual impairment, and 3/100,000 for neuronal ceroid lipofuscinosi. In the Nordic series, the prevalence for optic nerve atrophy was higher (15/100,000).

In the Finnish portion, the main disease groups of visual impairment were retinal diseases (35%), congenital malformations (33%), and neuro-
ophthalmological disorders (29%). At the same time, the corresponding proportion of retinal diseases in Sweden was only 14% and that of neuro-ophthalmological diseases 49% (Blohmé & Tornqvist 1997b). Most probably, children with cerebral visual impairment and additional systemic involvements were underregistered in Finland.

Congenital cataract was present in 11% of the Finnish children, 13% of the full-terms and 4% of the preterms. The disorder was more common in boys, as described in the Danish cohort in which the male/female ratio was 1.68 (Haargaard et al 2005). Unlike in the Danish cohort, older maternal age and low birth weight were not associated with congenital cataract in the Finnish study. The etiology of congenital cataract was genetic in around 50% of the Finnish cases, and in the other cases the etiology remained unidentified. The same levels of genetic causes for congenital cataract have been described in several western studies (Rahi et al 2000; Francis & Moore 2004).

The incidence of visual impairment due to congenital cataract did not change in Finland during the 1970–1980s, but thanks to early surgery, new microsurgical techniques with intraocular lens implantations, and effective postoperative rehabilitation the incidence is decreasing (Lundvall & Kugelberg 2002; Forbes & Guo 2006; Sotomi et al 2007). Visual impairment due to congenital cataract can often be avoided now, when treatments are started during the first 6 weeks after birth or at least during the first three months of life. Standardized screening protocols have been implemented at maternity units for the early identification and treatment of congenital cataracts (Foster & Gilbert 2003; Magnusson et al 2003).

Visual impairment due to retinopathy of prematurity was only seen in very immature infants, like in the other western countries with highly qualified health care (Fielder et al 1992). In a Canadian study, the proportion of retinopathy of prematurity was 43% in the birth weight group of ≤1000g and only 5% in the ≤1001g–2000g group (Archambault & Gomolin 1987). In our study, the diagnosis of visual impairment was retinopathy of prematurity in 100% of the children born at a gestational age of 20–24 weeks or with a birth weight of <1000g, but no child with retinopathy of prematurity was born at ≥33 gestational weeks. Thus, the international screening recommendations for retinopathy of prematurity have also been precisely correct for Finnish infants.

The prevalence of cerebral visual impairment (4/100,000) in the Finnish series was lower than in the Nordic series (8/100,000). It was also considerably lower than the present prevalence of 14/100,000 in the Finnish Register of Visual Impairment (Ojamo 2005). Most probably, enough attention was not paid to the cerebral causes of visual impairment in the 1970–1980s in Finland, and a considerable number of cases remained undetected. Cerebral visual impairment is known to be an increasing medical and social problem, associated with the high survival of very preterm infants suffering from neonatal asphyxia,
cerebral ischemia, intraventricular hemorrhages, hypoglycemia, and other metabolic disorders.

The incidence of cerebral hemorrhages in newborn children has decreased during the last decades, and improvements in the neonatal care very successful. The mean prognosis of preterm children, however, has not improved enough due to the rising birth rates of extremely low birth weight infants (Tommiska et al 2001). Even the children with less severe cerebral disorders have visuo-cognitive and behavioral problems and need multi-occupational long-term rehabilitation.

**Malformations**

Congenital malformations may be discovered despite no occurrence before the birth. The major part of the malformations (90%) develops in children with healthy parents without any predictive risks for malformations during pregnancy. We found congenital malformations present in more than a half of the children, and ocular malformations in a third.

Registers on congenital malformations, including ocular malformations, are maintained in many countries (Stoll et al 1997; Dolk 2005). According to Stoll et al (1997), the prevalence of congenital eye malformations was 75/100,000 in 1979–1988 in the French Registry of Congenital Malformations (Stoll et al 1992). The cases with visual impairment are not separately recorded in those registers, however, and they can not be used as the sources of visual impairment associated with congenital malformations. In our study, the prevalence of ocular malformations was 16/100,000. The Finnish Register of Visual Impairment was a valuable source of information on severe congenital disorders.

The etiology of congenital malformations is still unknown in 60%–70% of the cases, and their effective prevention is impossible. It is possible to detect 70%–80% of malformations by ultrasound screening during pregnancy. According to recent studies, genetic processes may be involved in half of the malformations, although the underlying mechanisms are still difficult to recognize and the influence of maternal infections may be more crucial than expected. Even consanguinity may still be a cause for congenital eye malformations (Grieshaber & Niemeyer 1998). The fertile population should be continuously informed about the harmful fetal effects associated with tobacco, alcohol, teratogenic drugs, and other environmental factors during pregnancy (Shepard et al 2002).

**Additional impairment and systemic diseases**

Additional impairments and systemic diseases were present in approximately 50% of the children in this study, including cognitive impairment in 39% of the cases and motor impairment in 33%. Cerebral palsy and epilepsy were common among the prematurely born and blind children. Similar and even higher prevalences of cognitive impairment have been described in earlier Nordic studies, e.g. 44% by Lindstedt (1972) and 50% by Warburg (1975).
Unfortunately, increased rates in children with combined visual and other impairment have been discovered in the 1990s (Nielsen et al 2007). The relative proportions of single ophthalmic diagnoses of visual impairment have differed in various European studies, but the same main diagnoses have been recorded from the 1950s through the 1980s. We found the percentages of cognitive impairment (53%) and motor impairment (55%) in preterm visually impaired children alarmingly high.

Blindness in children with cognitive impairment was investigated in the Netherlands in the 1950–1960s (Copper & Schappert-Kimmijser 1970). In their studies, neurologic disorders (39%), congenital malformations (30%), and prematurity (20%) were highly associated with visual impairment. Accordingly, neuro-ophthalmological causes with combined visual and cognitive impairment were already highly preponderant in Europe in the 1950–1960s, and the same situation continued through the 1970–1980s.

In South Germany, the prevalence of combined visual and mental impairment was 67/100,000 in children born in 1981–1987 (Häussler et al 1996). Lesions in anterior and posterior visual pathways coexisted frequently. The children often had motor impairment (80%) and epilepsy (67%). In our study, the prevalence of additional cognitive impairment was 19/100,000, i.e. a considerably lower than in many European investigations. It may be difficult to differentiate the primary local cause of vision loss, due to simultaneous injuries in anterior and posterior visual pathways and because of the lesions affecting posterior pathways are often followed by the transsynaptic retrograde degeneration with ultimate lesions also in the anterior pathways. Therefore, the diagnosis of visual impairment recorded in the patient histories in the first place may have varied from optic nerve atrophy to cerebral visual impairment, congenital nystagmus or more unspecified disorders.

In the German study by Häussler et al (1996) on visual impairment in mentally retarded children, the rate of preterm children was 29% and the main etiologies were perinatal in 41%, prenatal in 29%, and infantile-juvenile in 15%. In Finland, like in the other Nordic countries, perinatal causes were less common, but genetic and prenatal causes occurred more frequently. Both German and Nordic studies confirmed, however, that multiply handicapped children were more severely afflicted when their visual lesions originated from the perinatal period and they were less severely impaired in the cases with prenatal origins of the visual damage. Thus, prenatal etiologies were more common in the children with solitary visual impairment than in the cases with multiple handicaps (Study II).

Bothe et al (1991), from Germany, have also investigated ophthalmological disorders in children with combined visual and cognitive impairment during the 1960–1980s. According to their findings, the most common causes of visual impairment were optic nerve atrophy (24%), congenital cataract (17%), retinopathy of prematurity
(17%), malformations of ocular anterior segment (12%), and cerebral amblyopia (8%). Compared with the corresponding Finnish material, the visual impairment associated with congenital cataract and ROP may have been slightly more common in German children at the time.

**Full-term vs. preterm children**

Annual perinatal statistics have been published in Finland since 1987, when the Medical Birth Register was established in Helsinki by the National Research and Development Centre for Welfare and Health (Stakes). Approximately 5% of infants were born prematurely during the last three to four decades in Finland. Around 1% of the newborns have been very preterm infants, born prior to 32 gestational weeks, having significant risks for general morbidity as well as for visual impairment.

The causes of preterm birth have been investigated extensively. The following factors are known to influence preterm deliveries: maternal chronic disease, maternal infections, multiple pregnancy, earlier preterm births, spontaneous abortions, or stillborns, preterm placental detachment, preterm rupture of fetal membranes, prenatal uterine hemorrhages, pre-eclampsia, fetal malformation or growth retardation, difficult social conditions and low parental education, alcoholism, use of drugs, smoking, and young (<18 years) or old (>35 years) age of pregnant women. The basic mechanisms leading to preterm births are not thoroughly clear at the present time.

During 1972–1989 a total of 556 Finnish children with visual impairment were born and registered, of them 431 (77%) were full-term. In full-term children, the main causes of visual impairment were ocular malformations (34%), retinal diseases (31%), and neuro-ophthalmologic disorders (26%). The main diseases of visual impairment in prematurely born children were retinopathy of prematurity (46%) and neuro-ophthalmological disorders (39%). Retinopathy of prematurity developed in the most immature and sick infants. It was the cause of visual impairment in every newborn child with a birth weight of <1000g or with a gestational age of <25 weeks, but in no child born at ≥33 gestational weeks. These findings were similar to many other recent descriptions (Häussler et al 1996; Hussain et al 1999; Fledelius & Dahl 2000).

A significant difference in the visual and general outcome was shown between the full-term and preterm children. The rate of blindness was 40% in full-terms (vs. 70% in preterms), of systemic diseases 43% (vs. 64% in preterms), and multiple handicaps 45% (vs. 66% in preterms). Cognitive impairment occurred in 36% of the full-term children (vs. 53% in preterms) and motor impairment was present in 27% (vs. 55%). Auditory impairment was equally common (6%) in full-term and preterm children.

In the Hospital for Children and Adolescents of the Helsinki University Hospital, retinopathy of prematurity had developed in 17% of the preterm
children born between 1989–1991 (Lappi 1993). The median length of gestation had been 27 gestational weeks and the median birth weight 986 g. Only one child became blind. Fortunately, linear results have been achieved recently in all Finnish hospitals with qualified neonatal intensive care units. The incidence of retinopathy of prematurity has been decreasing and visual outcome in retinopathy of prematurity improved along with developments in neonatal care, regular eye screening programs for very low birth weight infants, and modern cryo and laser treatments for the threshold stage of retinopathy of prematurity (Fledelius & Dahl 2000; Fledelius et al 2000; Tommiska et al 2001).

**Male dominance**

Male children were prevailing in our study, likewise in many other previous studies (Norrie 1927; Lindstedt 1975; Schappert-Kimmijser 1975; Verloove-Vanhorick 1994; Blohmé & Tornqvist 1997a). A significant excess of males was also seen in the Danish register in the Nordic part of this study (Study IV).

The male excess associates with the diseases having a x-linked mode of inheritance, e.g. with x-chromosomal juvenile retinoschisis, ocular albinism, choroideremia, and x-linked congenital cataract. The x-linked inheritance does not explain the gender difference in total, however, and the basic cause of the male predominance is unfortunately unknown.

Males have been preponderant also in the cases with non-genetic optic nerve atrophy followed by perinatal complications. In the preterm children with optic nerve atrophy, the male/female ratio was as high as 2.18. The male excess seems to associate with the most severe cases of impairment, e.g. in children with combined visual, cognitive, and motor impairment after perinatal complications (Verloove-Vanhorick 1994; Gissler et al 1999).

In recent Swedish studies, the male dominance in children with perinatal complications has been even more pronounced (Blohmé & Tornqvist 2000). Genetic factors may also associate with unknown perinatal processes leading to severe visual disorders in boys (Study IV).

**Etiologies of visual impairment in children**

The main causes for childhood visual impairment in Finland were genetic, prenatal and perinatal factors. They had not changed crucially from the causes reported in European countries since the 1960s (Copper & Schappert-Kimmijser 1970). The causes were also rather equal in the Finnish and Nordic series of our study, i.e. genetic in 42% (vs. Nordic 40%), prenatal in 30% (vs. Nordic 26%), perinatal in 21% (vs. Nordic 22%), infantile-juvenile in 6% (vs. Nordic 10%), and unknown in 1% in both data.
Genetic origin of visual impairment is relatively common. Genetic causes of visual impairment and blindness have been also found in up to 50% of school children in German investigations (Lorenz 1996). Genetic visual disorders may be induced by infections, teratogens, and various environmental factors. They may also be related to older paternal age. Family history is negative in half of the genetic diseases and disorders caused by gene mutations are discovered unexpectedly in children with healthy parents (Nelson & Holmes 1989).

Some genetic diseases belong to the Finnish disease heritage, like neuronal ceroid lipofuscinosis and X-linked juvenile retinoschisis, which have been enriched in Finland due to “founder effects” and have a higher prevalence in Finland than in the other Nordic and western countries (Markkanen et al 1987; Järvellä 1991; Norio 1994; Mitchison et al 1995; Varilo et al 1996; Huopaniemi et al 1997; Huopaniemi et al 1999; Santavuori 2000; Hanein et al 2002; Varilo et al 2003). Therefore, when risks for severe hereditary diseases in the family exist, young couples need to be provided with genetic counseling, gene tests, and prenatal diagnostics (Goebel 1996, Rapola et al 1999).

Recent advances in molecular genetic technology have resulted in a progress towards the identification of disease genes (MacDonald et al 1998). Molecular genetic testing should already be carried out as an essential part of the clinical work in severe hereditary diseases with well-known genes and recognizable Finnish mutations, although specific gene therapies are still under clinical trials. Genotype-phenotype correlations have already been found, and they will probably help for selecting patients for gene therapies, e.g. in the cases with Leber’s congenital amaurosis (Hanein et al 2004).

Prenatal etiologies included an unfortunately high unspecified proportion (22%). Further understanding is urgently needed for riddles underlying disabling anomalies and functional disorders in the visual pathways (Kaukola et al 2005).

**Risk factors for visual impairment in children**

Prenatal (44%) and perinatal (46%) disorders were discovered often in the cases leading to visual impairment in Finnish children during the 1970–1980s. In addition to the preterm birth itself, significant risks for visual impairment had been caused by prenatal infections, birth asphyxia, neonatal respiratory difficulties, mechanical ventilation lasting over two weeks, and hyperbilirubinemia. Their development had been exceptionally common. Presently, neonatal serum bilirubin levels are followed up carefully in the Finnish neonatal care units according to the international
recommendations (Grönroos 2007). Too high bilirubin levels (≥340μmol/l) are treated by early phototherapy with blue-green light and by blood transfusion if necessary.

Various risk factors for preterm birth with associated visual impairment have been described, e.g. maternal diabetes and arterial hypertension, pre-eclampsia, prenatal uterine hemorrhages, multiple birth, previous preterm child, previous fetal malformations, use of alcohol and smoking during pregnancy, use of antibiotics over 14 days, mechanical ventilation over 96 hours, neonatal hypoxia and fluctuations in arterial oxygen levels, red blood cell transfusions more than seven units, etc. (Prendiville et al 1988; Flynn et al 1992; Gallo et al 1993; Penn et al 1995; Holmström et al 1998; Saarikoski 1998; Kekki et al 1999; Hussain et al 1999; Andres & Day 2000; Kekki et al 2001; Yang et al 2004; Yanovitch et al 2006).

The course of pregnancy is influenced by numerous biochemical, immunological, histopathological, anatomic, and infectious factors (Wilson-Costello et al 1998; Andres et al 2000). Infections alone may be associated with up to 40% of spontaneous preterm births, especially those taking place at an early gestational age. Also subclinical infections may have harmful effects on the course of pregnancy and on the fetal development. Warnings about smoking, alcohol, and drugs during pregnancy are useful for every age group. New medicines need to be avoided, until enough information on their safety has been achieved (Cleary et al 2005).

In a Swedish study on full-term children born in 1979–1998 with an unknown pre- or postnatal cause of impairment, risk factors for visual impairment were also placenta praevia, preterm placental detachment, breech delivery, over-term pregnancy (over 41 gestational weeks), and high birth weight (>4000g) (Tornqvist & Källen 2004). In our study, the mode of delivery could not be shown as a risk factor.

According to the British Columbia Health Surveillance Registry in Canada, including a total of 9,660 cases of birth defects, older paternal age increases the risk of congenital malformations and also the risk of congenital cataract (McIntosh et al 1995). Recent studies show, that the children born to elderly fathers have a 20% higher risk for genetic diseases with autosomal dominant transmission. Therefore, the American Fertility Society recommends an age limit of 50 years or less for semen donors (Plas et al 2000). Older maternal age (≥35) is associated with chromosomal defects, but it is not known to effect the neonatal outcome in other respects (Chervenak & Kardon 1991; Glaser et al 2003; Glaser & Jabs 2004).

**Visual and general prognosis of children**

The incidence of neuro-ophthalmological causes of visual impairment has increased since the 1960s, but the incidence of visual impairment due
to congenital cataract has clearly decreased during the last 15–20 years (Rosenberg et al 1996). Instead, the proportion of cerebral morphological and functional abnormalities has increased even in children born at full term. In Sweden, severe cerebral defects and dysfunctions were discovered in 74% of the full-term children with visual impairment born from 1989 to 1995 (Grönqvist et al 2001). The Swedish authors recommend cerebral imaging and pediatric consultations for every child with visual impairment. Because even minor cerebral disorders may influence the visuo-cognitive development and later school performance of the afflicted children, the cerebral disorders should be diagnosed early (Torrioli et al 2000).

Visual impairment due to retinopathy of prematurity has decreased since the 1990s along with improvements in the neonatal intensive care, the systematic ophthalmological screening for very low birth weight infants, and the introduction of cryo and laser treatments for threshold retinopathy of prematurity (Rosenberg et al 1996; Fledelius & Dahl 2000; Tommiska et al 2001; Chiang et al 2004; DiBiasie 2006; Christensen et al 2007). Presently, retinopathy of prematurity requiring treatment is very rare in infants with a birth weight >1500g. In the future, the progression of retinopathy of prematurity into a threshold stage may be further reduced by anti-angiogenic agents, capable of blocking the excessive production of vascular endothelial growth factors without interfering with the normal angiogenesis (Cooke et al 2004a).

Nowadays, blindness due to retinopathy of prematurity can be prevented with early laser treatment in most cases (Connolly et al 1998; Jandeck et al 2005). Even in infants with a birth weight of 500g–900g, the outcome has improved from that in the 1970–1980s (The Victorian Infant Collaborative Study Group 1997). Some researchers suggest, that the screening for retinopathy of prematurity could be restricted to more immature infants than presently, i.e. to infants born at 30 gestational weeks or lower and to infants with a birth weight of <1250g (Hutcheson 2003; Ahmed et al 2006). Unfortunately, rises in the incidence of retinopathy of prematurity have also been found in the 1990s, and therefore, restrictions in the eye screening have not been generally accepted (Svenningsen et al 1997; Holcroft et al 2003; O’Connor et al 2003; Wilson-Costello et al 2005). Thus, the retinal screening of preterm infants has still been started at the age of 4–6 weeks of life or between 31–33 gestational weeks (the sum of the gestational and postnatal weeks).

It is supposed, that the immediate perinatal period is the most dangerous one in relation to neonatal brain injuries (Cowan et al 2003). Despite improvements in perinatal care, the incidence of neurological sequelae in very preterm children has increased along with the higher survival rates of extremely low birth weight infants (Mikkola et al 2005; Stoelhorst et al 2005). A noteworthy increase in extremely low birth weight newborns
with a consequent rise in child morbidity has been found from 1983 to 1996–97 in the Netherlands (Stoelhorst et al 2005).

In Finland, only 26% of the infants in a national extremely low birth weight cohort from 1996–1997 had a normal general outcome at the age of 5 years, and major disabilities occurred in 20% of the children (Tommiska et al 2001). A later comparative study from 1999–2000 discovered no significant additional changes in the birth rate and the mortality of extremely low birth weight infants, although the incidences of intraventricular hemorrhages, respiratory distress syndromes, and septicemias seemed to have increased (Tommiska et al 2007).

Learning difficulties have been reported in 20–60% of very low birth weight infants (<1500 g). Even in cases without any diagnosed neonatal brain disorder, significantly lower scores have been recorded in perceptual motor skills, defects in spatial attention, poorer visual acuities, poorer or absent depth perception, and higher rates of strabismus in very low birth weight infants (Cooke et al 2004b). The disorders may associate with general abnormal cortical development as well as with perinatal focal lesions in the brain.

When compared with the earlier population-based studies, better results with improvements in the visual and general prognosis of extremely low birth weight infants born in 1999–2000, have been described in Norway (Markestad et al 2005). Encouraging results in the neurodevelopmental outcome of extremely low birth weight infants have also been described elsewhere, e.g. in children born in 2000–2002 in Cleveland, USA (Wilson-Costello et al 2007).

**Prediction of visual and general outcome**

The prediction of visual and other outcome of the children with neuro-ophthalmological disorders has been very problematic before the appearance of the new imaging technology. Nowadays it is known, that low Apgar scores 0–3 at birth do not necessarily predict neurological and visual impairment (Nelson & Ellenberg 1998). According to Nelson and Ellenberg (1998) in Philadelphia, 80% of the infants with an Apgar score 0–3 at 10 minutes had no neurological abnormality at the early school age.

Ultrasound technology was introduced in obstetrics in 1981. Ultrasound screening is a sensitive and safe method for the assessment of the fetal age and malformations. Approximately 70%–80% of congenital birth defects can be found by ultrasound screening during the first and second trimester of pregnancy. Nowadays, ultrasound screenings are performed twice per pregnancy in Finland, at the 13th–14th GWs and at the 18th–20th GWs. The latter screening is arranged especially for the detection of congenital
malformations. Fetal intracranial hemorrhages are also identified and categorized by antenatal sonography, and a fortunate decrease in the rates of fetal intracerebral hemorrhages from the 1980s has been discovered by ultrasound examinations (Ghi et al 2003; Ward & Beachy 2003). Ultrasound is also important at the follow-up of infants, especially in the cases of tiny preterms, which are too weak for magnetic resonance brain imaging.


Diffusion-weighted imaging (DWI) is a powerful additional method for the assessment of neonatal brain damage after suspected perinatal hypoxic-ischemic injury or for the prediction of abnormal neurodevelopmental outcome. A regular diffusion coefficient value during the first week of life does not guarantee that the tissue is normal, but repeated examinations during the first two weeks after birth give more reliable knowledge about the evolution of perinatal brain damage (Rutherford et al 2004).

Positron emission tomography (PET) can be used for the detection of perinatal cerebral hypoxia-ischemia in infants (Vannucci & Perlman 1997). Reliable information on the brain function of the full-term children with hypoxic ischemic encephalopathy has been obtained by positron emission tomography (Thorngren-Jerneck et al 2001). Findings during subacute periods after perinatal asphyxia have correlated with the short-term outcome of the afflicted children.

Developmental tests are used for defining visuo-perceptual impairments related to periventricular leukomalacia (Fazzi et al 2004). Significant correlations are found between neuroradiological and neuro-ophthalmological findings and the visuoperceptual profile at the age of 5–8.

**Future treatments**

Antiangiogenetic drugs and gene therapy may become beneficial new treatments for some serious childhood diseases (Grant et al 2001; Smith 2003; Cooke et al 2004a). It may be possible to prevent the development of threshold retinopathy of prematurity by blocking the excess production of vascular endothelial growth factors with new antiangiogenetic drugs.

Therapeutic gene deliveries in animal models have already led to progressive improvement in retinal function (according to electroretinography) and in retinal morphology, e.g. in Leber’s congenital
amaurosis (Frigg et al 2005; Min et al 2005; Bemelmans et al 2006). The results have given promise for beneficial human gene transfers as a photoreceptor-preserving treatment in the future.

**Health education**

Information on the dangers associated with pre- and perinatal infections and the use of tobacco, alcohol, and drugs during pregnancy must be included in the general health education for the population (Jaakkola et al 2001; Tikkanen et al 2006). According to reliable investigations, alcohol gets into the fetal circulation through the placenta and causes serious developmental disorders in the fetal central nervous system and in other organs (Halmesmäki & Autti-Rämö 2005). All parts of the visual system may be involved in the fetal alcohol syndrome. Microphthalmus, microcornea, Peters’ anomaly, cataract, persistent hyperplastic primary vitreous, colobomata, retinal dysplasia, and optic nerve hypoplasia have been diagnosed in fetal alcohol syndrome (Strömland 2004). Fortunately, we found only one child with fetal alcohol syndrome.

We have not recorded harmful fetal effects due to drugs or chemicals, but some cases may have been included in the cases with prenatal unspecified etiology. Some relatively common drugs have proved to be teratogenic, e.g. isotretinoin used for acne vulgaris (Honein et al 2001; Cheetham et al 2006). The most critical time is the first trimester of the organogenesis, i.e. the first 5–10 weeks from the last menses.

Women need to be most careful with medicines and other toxic substances as soon as the pregnancy has been identified. Especially the use of new drugs have to be avoided during the pregnancy. Information on harmful drug effects is available in the Finnish National Agency for Medicines and in the Family Federation of Finland in Helsinki (Malm 2002). Data on congenital malformations are collected in the Register on Congenital Malformations in the National Reseach and Development Centre for Welfare and Health (Stakes).

Prenatal diagnostics is possible for many severe diseases at present (Churchill et al 2000; Miny et al 2003). Induced abortion is possible on a medical basis until the end of the 20th gestational week, exceptionally until the end of the 24th gestational week, if a serious disease or anomaly has been diagnosed by amniotic fluid examination, chorion villus specimen, etc.

**Significance of the study**

For the first time, a reliable profile of childhood visual impairment was obtained in Finland. Criteria for further follow-up and international comparisons of data on childhood visual impairment were created by the
multinational group of Nordic ophthalmologists. The results will serve as basic data for follow-up studies on childhood visual impairment in Finland.

The registration of persons with visual impairment is compulsory for ophthalmologists in Finland, but some under-registration exists. It is not possible to estimate accurately the percentage of children with visual impairment born in 1972–1989, who possibly remained outside our study.

Children with other impairments and institutionalized children with severe mental and motor retardation have often remained unregistered, according to many reports (Warburg 1975; Gissler et al 1998; Blohmé & Tornqvist 2000). The Finnish data was in many respects well comparable with the data in other European countries (Foster & Gilbert 1992). The Finnish and the Nordic registers of visual impairment have been crucial sources of information with relatively low financial costs.

According to recent studies, some congenital ocular malformations and inherited ocular diseases are associated with advanced paternal age (Auroux 1992). Unfortunately, paternal age was not recorded in this study. Likewise, parental social class remained unrecorded, although it may have influenced the results, as it has influenced the perinatal health and the cumulative incidence of the intellectual disability (Gissler et al 1998b).

Valuable tools for furthering the prevention of childhood visual impairment were achieved by the analysis of the causes and the risk factors of visual impairment in Finnish children during the 1970–1980s. The importance of highly qualified antenatal, neonatal, and ophthalmological care was clearly proved and must be emphasized. It was also shown that further improvements will be possible with persistent efforts, changes in therapeutic models, and with continuous education for the health care personnel (National Research and Development Centre for Welfare and Health 1999 [Stakes]).
CONCLUSIONS

We evaluated the prevalence of visual impairment in Finnish children during the 1970s and the 1980s. Males were affected more often than females. Blindness was common, due to severe genetic diseases, congenital ocular and cerebral malformations, disorders during pregnancy, prematurity, and severe perinatal complications. The proportion of multihandicapped children was also high.

The etiology of visual impairment was genetic in 42% of cases, prenatal in 30%, perinatal in 21%, infantile-juvenile in 6%, and totally unknown in 1%. Thus, inherited diseases were the most prevailing causes of visual impairment in the Finnish children in the 1970–1980s. The susceptibility to pre- and perinatal infections may also be genetically programmed, resulting in neurological disorders and maldevelopments, even cortical malformations of the brain. Fortunately, new treatments for complicated hereditary diseases will probably be introduced in the following decades.

Prematurity was a major risk for severe visual impairment and blindness in children during the 1970–1980s. The incidence of visual impairment in the children born prematurely was seven times higher than the incidence of visual impairment in the full-term children. The incidence and the severity of retinopathy of prematurity did not decrease during the study period, not until in the 1990s along with crucial improvements in the neonatal and ophthalmological care. Due to the higher survival of very preterm infants, however, cerebral visual impairment with high rates of cognitive and motor impairment is still a difficult problem for the health care and the rehabilitation systems.

The causes of congenital malformations still often remain unspecified. Overwhelming new insights are needed for the clarification of the mechanisms leading to fetal anomalies with consequent severe visual and other disability.

Congenital cataract was the most common ocular malformation in children during the 1970–1980s. Unfortunately, no reduction in the incidence of visual impairment due to congenital cataract was seen until in the 1990s thanks to new methods in pediatric surgery. Likewise, resources for new treatments in pediatric ophthalmology need to also be guaranteed in the future.
The quality of maternity health care, pediatric ophthalmology, and pediatric neurology is under continuous evaluation. Medical, social, and educational costs associated with childhood visual and other impairments are high, and crucial improvements are constantly waited for. Continuous up-to-date health education is also needed for pregnant women, their spouses, and the population in general.
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## APPENDIX

Categories of visual impairment by World Health Organization (1973)

<table>
<thead>
<tr>
<th>WHO category of visual impairment</th>
<th>Visual acuity</th>
<th>Visual field diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO 1 Moderate VI</td>
<td>&lt;6/18–6/60</td>
<td></td>
</tr>
<tr>
<td>WHO 2 Severe VI</td>
<td>&lt;6/60–3/60</td>
<td></td>
</tr>
<tr>
<td>WHO 3 Profound VI</td>
<td>&lt;3/60–1/60</td>
<td>&lt;20 degrees, ≥10 degrees</td>
</tr>
<tr>
<td>WHO 4 Near-total blindness</td>
<td>&lt;1/60–light perception</td>
<td>&lt;10 degrees</td>
</tr>
<tr>
<td>WHO 5 Total blindness</td>
<td>No light perception</td>
<td>0 degrees</td>
</tr>
<tr>
<td>WHO 9 Unknown degree of blindness</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Low vision* WHO categories 1-2

*Blindness* WHO categories 3-5, 9