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Optic nerve hypoplasia: Risk factors and epidemiology

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ABSTRACT

Objectives: To study the epidemiology of optic nerve hypoplasia.

Design and Methods: Children with optic nerve hypoplasia and visual impairment were identified through the Swedish Register of Visually Impaired Children. Pre- and perinatal characteristics were obtained from the Medical Birth Registry and by scrutinizing pregnancy and delivery records. Clinical characteristics of children with optic nerve hypoplasia are described. The following risk factors were studied: maternal age, parity, maternal smoking, gestational duration, birth weight, delivery method, Apgar score, maternal disease during pregnancy, drugs used in early pregnancy.

Results: Young maternal age, first parity, maternal smoking, preterm birth and factors associated with preterm birth were risk factors for optic nerve hypoplasia. There was an indicated association with the use of fertility drugs and antidepressant drugs.

Conclusions: Optic nerve hypoplasia is apparently associated not only with other anomalies, notably of the central nervous system, but also with signs of general disturbance in fetal development.

Key words: optic nerve hypoplasia – epidemiology – risk factors – maternal age – smoking – drugs – prematurity

Optic nerve hypoplasia is a non-progressive congenital abnormality associated with a reduced number of axons in one or both optic nerves (Mosier et al. 1978). It can be bilateral or unilateral and is clinically characterized by a small optic disc, often surrounded by a peripapillary halo bordered by a dark ring of pigment. In addition, increased tortuosity of the retinal vessels as well as few branching points can be seen (Hellström et al. 1999). The pathogenesis is not fully understood, but the disorder can result from a number of still unidentified adverse events occurring during development of the visual pathways. The condition has been considered rare, but an increasing incidence has been reported during the last decades (Hoyt & Good 1992). The age-specific prevalence of visual impairment due to optic nerve hypoplasia in the Swedish population of 0–19 years is 6.3/100 000 (Blohmé & Tornqvist 1997c). The clinical picture reflects varying functional reduction ranging from very mild or no visual impairment to blindness (Björk et al. 1978; Lambert et al. 1987; Zeki & Dutton 1990). Optic nerve hypoplasia may occur as an isolated event or in association with other developmental anomalies, most often cerebral malformations (De Morsier 1956; Skarf & Hoyt 1984; Burke et al. 1991). A number of aetiological factors such as drugs (McKenna 1966; Chan et al. 1978; Hoyt & Billson 1978; Good et al. 1992), maternal diabetes (Patel et al. 1975; Peterson & Walton 1977; Donat 1981; Kim et al. 1989; Landau et al. 1998), and alcohol (Strömland 1987; Chan et al. 1991; Strömland & Pinazo-Duran 1994) have been associated with the development of optic nerve hypoplasia. Viral infections have also been implicated (Bistner et al. 1973).

Hitherto, however, no thorough investigation concerning risk factors for optic nerve hypoplasia in a nationwide population has been performed. In this study, we have explored possible risk factors responsible for the development of optic nerve hypoplasia in all Swedish children identified with this diagnosis and with a disease severe enough to cause visual impairment.

Material and Methods

Individuals with bilateral optic nerve hypoplasia severe enough to cause visual impairment were identified by inventory of the Swedish Register of Visually Impaired Children (Blohmé & Tornqvist 1997a). The analysis was restricted to individuals born during 1979–97.

The Swedish Register of Visually Impaired Children

This database includes data on all visually impaired children aged between 0 and 19 years in the country, with visual acuity (VA) of ≤0.3 and/or a simultaneous visual field defect. The Register was originally established by collecting data obtained from the medical records of low vision clinics and departments of ophthalmology throughout Sweden and is now continuously updated by reporting from these sources. Data obtained on each child are recorded on a standardized
form and subsequently entered into a database. Each record contains information on name, sex, date of birth, treating ophthalmologist, and low vision clinic, county, ophthalmological diagnosis, systemic diagnosis, aetiological factors, additional impairments, classification of visual impairment, visual field defects, refraction, near vision, and family history.

Suggested aetiological factors are divided into four main categories according to the system used in previous Nordic studies (Røsengen et al. 1992; Blohmé & Tornqvist 1997b), as follows:

(1) prenatal;
(2) perinatal;
(3) infantile/juvenile, and
(4) unknown.

Classification of visual impairment is made according to WHO (World Health Organisation) definitions. Ophthalmological diagnoses are classified according to a Californian version of ICD-9 (International Classification of Diseases, 9th version) (Risse et al. 1992; Hansen et al. 1992; Blohmé & Tornqvist 1997c).

On December 31, 1999 the database included data on 2774 individuals aged between 0 and 19 years. The total Swedish population aged between 0 and 19 years was then 2.25 million out of an entire population of 8.86 million. A mong infants with a diagnosis of optic nerve hypoplasia, infants with Down syndrome and infants with incomplete personal identification numbers were excluded.

The Medical Birth Registry

Cases with a complete personal identification number were matched with the Medical Birth Register for 1977-97. This register was started in 1973 and contains data on antenatal care, delivery, and the paediatric examination of newborn children (Cnattingius et al. 1990). Since 1982, it has been based on copies of the original medical records, computerized by the National Board of Health, Stockholm.

Information on drug use in early pregnancy was obtained from the records of the 100 women whose antenatal care records could be retrieved. The same form is used throughout Sweden. Pregnant women are interviewed by their attending midwife early in their antenatal care (usually in weeks 10-12), and are asked about smoking habits and drug use during the pregnancy, among other issues.

Statistical analysis

Various risk factors were compared between cases and between all infants born (n = 2109316). Risk estimates were determined as odds ratios (OR) using M antel-Haenszel procedure after various stratifications, and 95% confidence intervals (95% CI) were estimated using Miettinen's test-based method. In order to study a putative trend in maternal age distribution, a weighted linear regression analysis of the log (OR) was carried out.

The following risk factors were studied:

(1) maternal age and parity;
(2) maternal smoking in early pregnancy;
(3) gestational duration;
(4) birth weight and birth weight for pregnancy week;
(5) maternal diabetes;
(6) maternal pre-eclampsia;
(7) drug use in early pregnancy;
(8) fetal presentation;
(9) delivery method, and
(10) low Apgar score at 5 min.

Birth weight for each pregnancy week was expressed as standard deviations (SD) of the expected birth weight at each week according to a sex and parity specific normal growth curve (Källén 1995). Infants with a birth weight less than 2SD below the expected mean were regarded as small for gestational age (SGA).

No information on drug use among women with normal infants was retrieved in the study. Comparisons were instead made with data from the Medical Birth Registry, where records of drug use in early pregnancy have been computerized since 1994. This information is based on the same source as that used in the present study, and at least crude comparisons can be made.

Results

A total of 156 individuals (72 male and 84 female; sex ratio 0.86, 95% CI = 0.62-1.17) with optic nerve hypoplasia were found in the database of visually impaired children. Among these, 63 (40%) had an isolated optic nerve hypoplasia without any systemic diagnosis. A total of 39 had reported congenital cerebral malformations, and of these 13 displayed septo-optic dysplasia and another six showed other mid-line deficiencies such as agenesia of the corpus callosum. A dditionally 28 had diagnoses such as encephalopathy or cerebral palsy, indicating associated cerebral damage. A togetter, 43% of subjects showed signs of cerebral involvement.

As expected, prenatal aetiologies were by far the most commonly suggested ones and occurred in 125 of the individuals. Of these, 104 were aetiologically classified 'prenatal unspecified'. The aetiological classification in 26 cases was perinatal, and in five cases it was unknown (Table 1). Aditional impairments occurred in 98 individuals (63%), for whom a combination of mental and motor impairment was the most frequently occurring (27%) (Table 2). Reduction in visual acuity varied considerably (Table 3). A total of 17 individuals (11%) had no light perception, whereas 42% of cases fell into WHO category 1 or had VA of 0.3. The proportion of blindness according to WHO criteria was 32%.

Records for a total of 125 children with optic nerve hypoplasia matched with data obtained from the Medical Birth Registry and could be analysed. Matching proved impossible in 23 cases because the subjects did not have complete identification numbers in the Registry of Visually Impaired Children (due to registration routines in one particular area of Sweden). The children in the remaining cases had either not been registered in the Medical Birth Register (occurs in 1-2% of all infants born) or had not been born in Sweden but had immigrated or had been adopted from abroad.

Among the matched children, there were three twins (1.6%) and thus 122 singleton births.

Table 4 shows ORs for maternal age, parity and maternal smoking, with each factor stratified for year of birth and the other two factors. There is an increased risk for low maternal age (independent of parity) and a statistically significant declining trend with age (p < 0.01) and for first parity (independent of age), compared with higher parity. There is also an increased risk for parity 4+, although this does not reach statistical significance. Maternal smoking in early pregnancy is a risk factor and a dose-dependency is indicated. The effects of smoking were analysed in infants with a birth weight below 2500g and infants with a birth weight of 2500g or more. In the latter group, the effect of smoking was further increased: OR = 1.73 (95% CI 1.10-2.72) for any smoking and OR = 2.19 (95% CI 1.23-3.88) for smoking 10 or more cigarettes.
A study was conducted to identify risk factors for optic nerve hypoplasia among 156 Swedish children/adolescents. No risk increase was noted for any smoking in low birth weight infants (OR = 0.86, 95% CI 0.35–2.13).

Preterm birth (<37 completed weeks) among singletons showed an OR of 3.47 (95% CI 2.25–5.35) and low birth weight (<2500g) an OR of 4.96 (95% CI 3.27–7.52). The OR for being SGA was 2.63 (95% CI 1.42–4.86). All these ORs were stratified for year of birth, maternal age, parity, and smoking habits.

Only one woman was diagnosed with diabetes. The expected number was 0.4. Four women reported a period of subfertility before the pregnancy. Maternal pre-eclampsia occurred in only four women with singleton births.

The OR for having a caesarean section (based on 32 cases versus non-instrumental vaginal delivery in singleton deliveries) was 2.98 (95% CI 2.02–4.40), but after stratification for gestational duration, the OR decreased to 2.55 (95% CI 1.63–3.99). Instrumental vaginal delivery versus non-instrumental vaginal delivery showed an OR of 1.00 (95% CI 0.43–2.34) after stratification for gestational week. Among singleton vaginal deliveries, only four were breech deliveries. Breech versus head presentation (stratifying for gestational week) showed an OR of 1.55 (95% CI 0.54–4.45) (this analysis was restricted to the period 1982–97 for technical reasons).

Low Apgar scores (<7 at 5 min) were noted in eight singletons. The OR versus Apgar score ≥7 was 3.90 (95% CI 1.96–7.75).

According to the antenatal records for the 100 women whose records were scrutinized, drug use was reported by 37 women, and included a total of 45 drugs (see Table 5). Among these, the following can be commented upon.

One woman used an antifungal drug (griseofulvin). Three women had become pregnant after drug treatment for infertility: bromocriptine (1), cyklofenil (1), and clomifene (1). Four women used drugs related to manic-depressive disease: lithium (1), clomipramine (2), and citalopram (1). All drugs used are accounted for in Table 5.

In the course of scrutiny of antenatal records, it was found that one infant had two previous sibs with microcephaly and another infant had a previous sib with a mid-line defect.

Discussion

Our study identified a number of risk factors for optic nerve hypoplasia. Low mat

Table 1. Distribution of suggested aetiological factors among 156 children/adolescents with bilateral optic nerve hypoplasia.

<table>
<thead>
<tr>
<th>Aetiological groups and subgroups</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal aetiology</td>
<td>125</td>
</tr>
<tr>
<td>Genetic without chromosomal cytogenetic aberration</td>
<td>5</td>
</tr>
<tr>
<td>Genetic with chromosomal cytogenetic aberration</td>
<td>8</td>
</tr>
<tr>
<td>Infectious disease, prenatal</td>
<td>4</td>
</tr>
<tr>
<td>Intoxication</td>
<td>2</td>
</tr>
<tr>
<td>Other prenaatal influence, specified</td>
<td>2</td>
</tr>
<tr>
<td>Other prenaatal influence, unspecified</td>
<td>104</td>
</tr>
<tr>
<td>Per/neonatal aetiology</td>
<td>26</td>
</tr>
<tr>
<td>Maturity with asphyxia</td>
<td>10</td>
</tr>
<tr>
<td>Maturity, other peri-neonatal complications</td>
<td>6</td>
</tr>
<tr>
<td>Prematurity with dysoxygination</td>
<td>5</td>
</tr>
<tr>
<td>Prematurity with other complications</td>
<td>5</td>
</tr>
<tr>
<td>Unknown time and cause</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2. Distribution of additional impairments among 156 Swedish children/adolescents with bilateral optic nerve hypoplasia.

<table>
<thead>
<tr>
<th>Impairments</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental (exclusively)</td>
<td>24</td>
<td>(15%)</td>
</tr>
<tr>
<td>Mobility (exclusively)</td>
<td>12</td>
<td>(8%)</td>
</tr>
<tr>
<td>Hearing (exclusively)</td>
<td>3</td>
<td>(2%)</td>
</tr>
<tr>
<td>Mental and mobility</td>
<td>42</td>
<td>(27%)</td>
</tr>
<tr>
<td>Mental and hearing</td>
<td>5</td>
<td>(3%)</td>
</tr>
<tr>
<td>Mobility and hearing</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mental, mobility and hearing</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other impairments</td>
<td>10</td>
<td>(6%)</td>
</tr>
<tr>
<td>Total additional impairments</td>
<td>98</td>
<td>(63%)</td>
</tr>
</tbody>
</table>

Table 3. WHO classification of visual impairment and the distribution of visual acuities among 156 Swedish children/adolescents with bilateral optic nerve hypoplasia.

<table>
<thead>
<tr>
<th>Category</th>
<th>Vision</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low vision 0.1-0.3</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>0.05-0.1</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>Blindness 0.02-0.05</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>&lt;0.02</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>No light perception</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>Unknown</td>
<td>19</td>
</tr>
<tr>
<td>&gt; = 0.3</td>
<td>Reference</td>
<td>10</td>
</tr>
</tbody>
</table>
eral age (irrespective of parity) and low parity (irrespective of age) were both risk factors. Maternal smoking was an independent risk factor. Among the risk factors reflected by infant characteristics are preterm birth, low birth weight and being small for gestational age. Analysis of drugs used during pregnancy indicated risk associated with fertility drugs and antidepressant drugs.

The characteristics of the infants with optic nerve hypoplasia in the present material mainly agree with those found in smaller published studies. Our study found the condition to occur at a rate of seven per 100 000 births, higher than the 1.8–6.3 per 100 000 births described in the literature (Jan et al. 1977; Blohmé & Torqvist 1997c). However, it has been suggested persuasively that the disease may be more prevalent than previously thought (Lambert et al. 1987). The actual occurrence of the condition is certainly still higher than that shown here, as our study was restricted to serious cases involving visual impairment (Table 3). Infants with milder forms of optic nerve hypoplasia may either not have any visual impairment, or the condition may be unilateral.

Optic nerve hypoplasia is characterized in the literature as a congenital malformation of prenatal origin (Taylor & Stout 1997). It is often seen together with septo-optic dysplasia and other cerebral malformations (De Morsier 1956; Skarf & Hoyt 1984; Burke et al. 1991). We found a high proportion of infants (63%) with additional impairments, although this is not surprising given the high rate of associated cerebral involvement. Burke et al. (1991) found neuro-developmental handicaps in 32 of 46 children (70%) with optic nerve hypoplasia, but described structural central nervous system abnormalities in 90% of them.

Our study found a sex ratio of 0.87, thus a predominance of females. The sex ratio does not differ significantly from that in the age-specific population (1.06), but it differs from that previously reported by Zion (1976), who found a sex ratio of 1.5 in a review of the existing significant literature in English on the subject.

As stated earlier, some aetiological factors have been suggested in the literature, notably maternal diabetes and maternal alcoholism. Landau et al. (1998) found that 8.8% of children of mothers with diabetes had optic nerve hypoplasia. In our study, only one mother was diabetic. Children of diabetic mothers present superior segmental hypoplasia with normal or very limited decrease in visual function (Peterson & Walton 1977; Kim et al. 1989) and the material we present consists of children with visual impairment. We have no data on maternal alcoholism, but none of the medical histories of the 100 cases scrutinized contained notes on alcohol or drug abuse. Optic nerve hypoplasia has been estimated to occur in as many as 48% of infants with fetal alcohol syndrome (FAS) (Strömland 1987). Given an incidence of FAS of 1/600 (Olegård et al. 1979), this would mean that the rate of optic nerve hypoplasia associated with FAS would be 80 per 100 000 births, a rate which does not seem realistic even if mild forms are included.

We found an increased risk of optic nerve hypoplasia in infants born of smoking women. The association between maternal smoking and infant congenital malformation is much debated but, at least for some conditions, association exist which are probably causal (Källén 2001). The association between maternal smoking and optic nerve hypoplasia is dose-dependent and remains after stratification for birth weight, indicating a direct toxic effect. Some authors have suggested that maternal drug use can cause optic nerve hypoplasia, generally based on single case reports. In our study, we found relatively rare drugs occurring more than once for two groups: drugs used for treatment of infertility (three cases) and drugs used for treatment of depressive disease (four cases). These findings may be random, but if not, they explain only a small number of cases. During 1995–99, antidepressant drug use in early pregnancy was reported by seven per 1000 pregnant women; the finding that three mothers of infants with optic nerve hypoplasia used antidepressants during pregnancy is therefore noteworthy, but more data are needed in order to verify or reject an association. One woman reported the use of the antifungal drug griseofulvin, which has been associated with birth defects. In the 1995–99 M edical Birth Registry, only one woman reported use of griseofulvin. Table 5 shows exposures for commonly used drugs such as antibiotics, anti-asthmatics, and analgesics that mirror their use in the general population.

Other maternal characteristics found to be risk factors for optic nerve hypoplasia include young maternal age (irrespective of parity) and low parity (irrespective of age). Some previous studies, all of which were smaller than the present study, have also observed that young maternal age and first parity may be over-represented (Elster & M C Arney 1979; Purdy & Friend 1979; M argalith et al. 1984; Robinson & Conry 1986). Young maternal age is a risk factor for a few congenital malformations, the most well-known of which is probably gastroschisis (Källén & Lindham 1982). Optic nerve hypoplasia may be a malformation to be added to this list.

Preterm birth, low birth weight, SGA, low Apgar scores, and caesarean section are all associated with an increased risk for optic nerve hypoplasia. Assuming that the condition does not originate during birth, but is a congenital malformation formed much earlier, these associations could be due to unfavourable conditions during development, affecting fetal growth, general fetal development and the risk of malformation. Early fetal maldevelopment might be associated with an increased risk of peri-neonatal complication.

Another possibility is that optic nerve hypoplasia actually results from preterm birth and the complications associated with such births. Optic nerve atrophy might be more commonly expected, as a result of neonatal ischaemia. It is possible that some misclassification has occurred, but it can hardly be significant enough to account for the results seen here. Apart from causing visual impairment, optic nerve hypoplasia can be associated with endocrine disturbances (Hoyt et al. 1970; Skarf & Hoyt 1984; Brodsky &

### Table 5. Drug use recorded in antenatal medical records for 100 women whose children developed optic nerve hypoplasia.

<table>
<thead>
<tr>
<th>Drug category</th>
<th>Number of drugs</th>
<th>Number of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal drugs</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Insulin</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>A ntifungal drugs</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>O vulation stimulator</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>A ntibiotics</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>M uscle relaxants</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>A nalgesics</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>L ithium</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>A ntidepressants</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Common cold drugs</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>A nti-asthmatic drugs</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>A nti-nausea drug</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>E ye drops</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Glaser (1993). Sudden death in children with septo-optic dysplasia has been reported (Brodsky et al. 1997) and it is thus of vital importance that optic nerve hypoplasia is recognized and that appropriate further investigation is performed. The increasing incidence and the intriguing pathogenesis illuminates the importance of epidemiological studies and the evaluation of possible risk factors as part of preventive work.

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