The Epidemiology of Anophthalmia and Microphthalmia in Sweden.

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Abstract

Infants with a clinical diagnosis of anophthalmia or microphthalmia were identified from four health registers in Sweden, covering different parts of the period 1965-2001. During the observation period, the rate of anophthalmia decreased from the early 1970s from 0.4 to 0.2 per 10,000 births. The registered rate of microphthalmia increased markedly during the observation period to reach a maximum in 1987 of about 1.5 per 10,000. About 10% of the 432 identified children had a chromosome anomaly. There was no geographical variation in prevalence and infants born in urban or rural districts had, if anything, a lower risk than infants born in cities (0.93 and 1.13 per 10,000, respectively). Non-eye malformations were more common at anophthalmia (63%) than at microphthalmia (30%). Sex ratio was normal and no statistically significant variation between sub-groups (anophthalmia, microphthalmia, isolated, associated with non-eye malformations) could be demonstrated. There was a marked risk increase with maternal age but no certain parity effect, no effect of maternal education, but a possible association with subfertility. Maternal smoking in early pregnancy seemed to increase the risk for anophthalmia or microphthalmia in the absence of a coloboma.

Key words: anophthalmia, microphthalmia, epidemiology, maternal age, smoking.

Introduction

Relatively little is known about the epidemiology of anophthalmia and microphthalmia. Data from the International Clearinghouse for Birth Defects Monitoring Systems [1] showed a ten-fold variability in the registration of birth prevalence of these malformations, from a low rate of 0.22 per 10,000 in England-Wales to a high rate of 2.56 per 10,000 in Metropolitan Atlanta. Most programmes reported rates around 1 per 10,000. Table 1 summarizes some pertinent studies in the field.

The report of a cluster of infants with an- or microphthalmia in Britain which was linked to the use of a pesticide, Benomyl, initiated the compilation of a national register of babies born with an- or microphthalmia in England, 1988-1994, described and analyzed by Busby e al. [7] and Dolk et al. [8].
Except for the suggested effect of Benomyl, few exogenous factors (such as radiation, maternal infections, diabetes, alcohol, and thalidomide) of importance for the aetiology of an- or microphthalmia have been discussed, see review by Strömland et al. [9].

The purpose of the study was to identify risk factors for anophthalmia or microphthalmia and to describe the epidemiology of these malformations. The recording of risk factors were made before the the presence of an eye malformations were known and is therefore prospective.

Material and Methods

The material for this study was collected from four different sources in order to get as complete ascertainment as possible, at least for part of the observation period.

1) The Swedish Registry of Congenital Malformations (Källén and Winberg, [10]) started in 1965 but up to and including 1972, one county did not participate in the registration. Only relatively serious malformations should be reported. Infants with chromosome anomalies are registered as such and only from 1983 onwards were also specific structural malformations registered in infants with abnormal chromosomes. Data up to and including 2001 were used.
2) The Medical Birth Registry (Cnattingius et al. [11], The Swedish Medical Birth Registry 12]) contains medical data on nearly all infants born in Sweden since January 1, 1973. Data from maternal health care, delivery units, and the paediatric investigation of the new-born including malformation diagnoses. From this register, information on maternal age, parity, smoking habits in early pregnancy (from 1983 onwards), maternal diseases, maternal education, years of involuntary childlessness before the pregnancy as an estimate of subfertility (from 1983 onwards), and maternal chronic diseases were obtained. The smoking and subfertility information is obtained from midwife interviews in early pregnancy. Maternal education was linked (up to and including 1995) from the Education Register (Statistics, Sweden).
3) The Hospital Discharge Register contains discharge diagnoses of all in-patients in Sweden since 1987 up to and including 2000.
4) The Register of Visually Impaired Children (Blohmé and Tornqvist [13]) contains information on all children with a visual impairment (visual acuity <0.3 and/or visual field defect) and 0-19 years of age. This register was available for infants born in the period 1981-2001 and investigated before the end of 2002.

In order to identify as many infants with an- or microphthalmia as possible, data from all four registers were added to form a master file and duplicate entries were removed. Diagnoses of non-eye congenital malformations or chromosome anomalies were added from all four registers. Immigrant children were excluded from the study. All data on the characteristics of the mothers were exclusively obtained from the Medical Birth Register and studies of risk factors were made by a comparison with all infants registered in the Medical Birth Registry.

Cases consisted of infants with a diagnosis of anophthalmia or microphthalmia. The presence of a coloboma with microphthalmia was also marked. In the Registry of Congenital Malformations and the Medical Birth Registry, microphthalmia was a clinical diagnosis as recorded at the clinical examination by the examining paediatrician. In the Register of Visually Impaired children, the diagnosis was based on ophthalmologic examination. In the Hospital Discharge Register, the origin of the diagnosis depended on the type of clinic, paediatric or ophthalmologic, where the child had been cared for.

Cases were divided into the following groups:
1) chromosome anomaly recorded in one or more register.
2) infants with only an eye malformation (isolated)
3) infants with also non-eye malformation(s) (non-isolated)

For prevalence studies, all available data were used. For studies of risk factors identified from the Medical Birth Registry, only the period from 1973 onwards (1983 onwards for some variables) could be used. This part of the study was restricted to the 317 infants without chromosome anomalies which linked to the Medical Birth Registry (97% of all).

Statistical analysis was performed by chi-square tests or by Fisher´s exact method for analysis of 2x2 tables. For adjustment of confounders, Mantel-Haenszel technique was used. Odds ratios (OR) were estimated and 95% confidence intervals (95%CI) were determined. In

Fisher tests, exact estimates of 95%CI were made, in Mantel-Haenszel analyses, a test-based method (Miettinen) was used. When the expected numbers were small, observed and expected (after adjustment for various factors) were compared based on Poisson distributions.

Two stratified ORs were compared with *z* tests based on the variances obtained from the stratified analyses [14].

Results

A total of 266 cases were identified from the Registry of Congenital Malformations (1965-2001). Together with the Medical Birth Registry, 359 cases were identified. These two registers are based on neonatal diagnoses. By adding cases only identified from the Hospital Discharge Register or the Register for Visually Impaired Children, a total of 432 cases were identified.

Among the 432 children, 44 had an identified chromosome anomaly. All infants had not been subjected to chromosome analysis but the infants with identified chromosome anomalies in most instances had well-defined chromosome syndromes like trisomy 13, 18, or 21. It is not known how many infants actually were studied with a cytogenetic analysis.

The remaining analysis was restricted to the 388 children without any known chromosome anomaly. Among them, 107 had a diagnosis of anophthalmia (8 of them also microphthalmia) and 281 had a diagnosis of microphthalmia but not anophthalmia (44 had also a diagnosis of coloboma).

Prevalence at birth

Figure 1 shows the frequency of identified infants with anophthalmia or microphthalmia during the period 1973-2001. Before 1973, the only data source was the Registry of Congenital Malformations which most likely was incomplete. There was a steady decrease in the rate of infants with anophthalmia since 1973 from a maximum of 0.4 down to about 0.2 per 10,000 births. The graph for microphthalmia showed a marked increase up to about 1987, followed by a decrease. The maximum value for microphthalmia indicated a rate of about 1.5 per 10,000 births when all available registers were used.

Geographic distribution

The cases were distributed accorded to county of birth (24 counties in Sweden) and also according to type of municipality where the infant was born: rural areas, urban district, cities. Urban districts represent densely populated areas without town characteristics.

There was no statistically significant difference between counties (adjusting for type of municipality): the chi-square for 23 d.f. was 20.9, p=0.64.

Among 470,707 infants born in rural municipalities, 44 had an- or microphthalmia, 0.93 per 10,000 born. The corresponding numbers for infants born in urban districts was 31 cases among 332,553 born, 0.93 per 10,000. Among 2,124,864 infants born in cities, 240 had an- or microphthalmia, 1.13 per 10,000. These rates do not differ significantly (chi-square at 2 d.f. = 2.08, p=0.35).

Associated non-eye malformations

Among infants without a known chromosome anomaly, non-eye malformations were present in 152 of the 388 children (39%),
63% for anophthalmia (67/107) and 30% for microphthalmia (85/281). The OR for having non-eye malformations was 3.86 (95%CI 2.38-6.34) in infants with anophthalmia compared with infants with microphthalmia.

Visual acuity and additional impairments

Table 2 summarises data on the 78 infants with bilateral anophthalmia or microphthalmia and reported to the Register of Visually Impaired Children (binocular visual acuity <=0.3). That information was not available for children, not reported to this register.

Infant sex

Among all infants with an- or microphthalmia and known sex (excluding chromosome anomalies), 197 were male and 190 female, a sex ratio of 1.04 (95%CI 0.85-1.27), close to the normal sex ratio of 1.06. Infants with isolated anophthalmia had the lowest sex ratio (0.69) but it could still estimate the normal ratio. If stratification is made for type of eye malformation, the sex ratio among non-isolated cases was higher than that among isolated cases (OR =1.50, 95%CI 0.98-2.30) but statistical significance was not reached (p=0.06). If instead stratification was made for isolated/non-isolated, there was no difference between anophthalmia and microphthalmia (OR = 1.08, 95%CI 0.67-1.73).

Multiple birth

Among the infants with anophthalmia or microphthalmia there were nine infants born as twins (only one twin affected). Among the nine twin pairs, six were like-sexed and three unlike-sexed. There were no higher order multiples. The odds ratio for being born as a twin was 1.28 (95%CI 0.66-2.48) after stratification for year of birth and maternal age.

Maternal age and parity

Table 3 shows the odds ratio estimates for maternal age (stratified for year of birth and parity) and for parity (stratified for year of birth and maternal age). Each group is compared with all other groups.

There was an increased risk with increasing maternal age. It could be due to the inclusion of infants with unidentified chromosome anomalies. Such infants were likely to have non-eye malformations and we therefore compared the risk at high maternal age between affected individuals with and without non-eye malformations. The OR for a maternal age of 35 years old or more was 1.33 (95%CI 0.63-2.82) for infants with non-eye malformations and 2.11 (95%CI 1.23-3.62) for infants without such malformations. These two odds ratios did not differ significantly ($z=0.98$, $p=0.25$).

The OR for a maternal age of 35 years or more for infants with anophthalmia (1.97, 95%CI 1.22-3.58) did not differ significantly from that for infants with microphthalmia (1.72, 95%CI 1.09-2.71, $z=0.40$, $p=0.37$).

There was no certain parity effect after adjustment for year of birth and maternal age.

Maternal education

As an estimate of socio-economic level, maternal education level was analysed, restricted to the period 1973-1995 (278 cases). Women with no information on education differed with respect to risk for infant an/microphthalmia from women with known education after stratification for year of birth, maternal age and parity. The OR for each educational level, stratified for year of birth, maternal age, and parity, varied between 0.65 (95%CI 0.35-1.23) at <7 years compulsory school to 1.12 (95%CI 0.79-1.59) for more than 3 years post-gymnasium education. When women with full gymnasium education were compared with women with shorter education, the OR was 1.03 (95%CI 0.79-1.33), nearly identical for anophthalmia (1.05) and for microphthalmia (1.03). Gymnasium in the Swedish school system corresponds roughly to upper secondary school in UK and senior high school in USA.

Maternal subfertility

Maternal subfertility was identified from reported years of involuntary childlessness. Among 204 cases born after 1982 (when this variable began to be recorded), 16 reported a period of involuntary childlessness. After stratification for year of birth, maternal age, and parity the OR for subfertility was 3.62 (95%CI 0.77-17.2). The increased OR can thus be random.

Maternal smoking

The effect of maternal smoking was also studied for the 204 infants born after 1982. The OR for any smoking was for all cases 1.21 (95%CI 0.86-1.70). Among 37 of the cases, the presence of a coloboma was marked. The OR for smoking among the remaining 167 cases was 1.33 (95%CI 0.92-1.91). If the 16 infants whose mothers reported involuntary childlessness were removed, the OR increased to 1.47 (95%CI 1.01-2.14). The reasons for these step-wise reductions are given in the Discussion.

Maternal chronic diseases

Maternal diagnoses as recorded in the Medical Birth Registry, were analysed for the period 1973-2001. The number of women with a diagnosis of diabetes and an infant with an- or microphthalmia was 4 - the expected number, stratified for year of birth, age, and parity, was 1.5 (RR = 2.6, exact 95%CI 0.7-6.7). None of the women whose infant had an- or microphthalmia had a diagnosis of epilepsy (0.3 expected).

Discussion

Anophthalmia and microphthalmia may have different pathogenesis. A complete absence of eyes can be the result of an early disturbance of the neural plate but often anophthalmia really represents a very strong microphthalmia - the eye remnants can only be identified after histological examination of the orbital content. The term "clinical anophthalmia has been coined by Clement et al. [2], stressing this condition. Microphthalmia is the result of reduced growth of the eye ball and is sometimes secondary to a closure defect of the choroidal fissure, resulting in a coloboma. It is possible that different etiological factors exist for coloboma malformations than for microphthalmia which is a result of disturbed eye ball growth. In a proportion of infants with microphthalmia, a diagnosis of coloboma was also given, but the

absence of a coloboma diagnosis does not necessarily mean that no coloboma was present.

Rate comparisons are hampered by the fact that in any register of congenital malformation of a size large enough to permit studies of rare malformations like anophthalmia or microphthalmia, ascertainment is seldom complete and may vary between different registers. We used four separate registers and hopefully identified most clinically important cases but mild cases may well be missing. For the analysis of risk factors, total ascertainment is not necessary but the findings made may refer specifically to more severe forms.

The recorded rate of anophthalmia (see Figure 1) showed a steady decrease. In agreement with most published studies, the average rate is around 2-3 per 10,000 births.

The rate of microphthalmia continued to increase during the observation period up to 1987 and then began to decrease. The maximum value of about 1.5 per 10,000 is in agreement with the highest rates recorded in the literature (Table 1). The rate increase was partly a result of the inclusion of data from the Register from Visually Impaired Children (data from birth year 1981 and onwards) and from the Hospital Discharge Register (which began in 1987). Even before these registers became active, however, a marked increase in the registration was noticeable. The difficulties in the complete identification of infants with microphthalmia has been stressed previously by Källén et al. [5].

Some studies have searched for clustering or an uneven geographical distribution of infants with an- or microphthalmia without success. In a study from England[8], no statistically significant regional or district variability in prevalence was found but a higher risk in rural than in other areas. In the present study no significant geographic variability was found. In the present study the rate in cities was slightly but not significantly higher than in urban or rural areas. The difference in results may have many explanations. A large part of the rural area in Sweden in not used for agriculture but represents forests. Furthermore, use of

chemicals in Swedish agriculture is relatively restricted.

A low sex ratio in infants with eye malformations has been described by Stoll et al. [3] but a normal sex ratio was found by Källén et al. [5]. We found a higher sex ratio among infants with associated non-eye malformations than in infants with only anophthalmia or microphthalmia, and a low sex ratio in isolated anophthalmia. These variations in sex ratio could, however, be random.

An increased rate of twinning was noted by Källén et al. [5]. This was indicated also in the present study but statistical significance was not reached.

We found high maternal age to be a risk factor for anophthalmia and microphthalmia which agrees with data published by Källén et al. [5]. Such an effect could be the result of the inclusion of unidentified chromosome anomalies but this is less likely as the odds ratio did not differ between isolated and non-isolated cases.

A weak and non-significant effect of parity 1 was seen - this could be an effect of an association with subfertility because parity effect was studied after standardisation for age and a subfertile couple will as an average have an infant later than a couple with normal fertility. Subfertility appeared as an indicated risk factor for anophthalmia or microphthalmia but statistical significance was not reached.

Maternal education as an indicator of socio-economic level showed no clear-cut association with these malformations which agrees with findings from UK according to Dolk et al. [8].

Maternal smoking has been associated with some congenital malformations as reviewed by Källén [14]. Little is previously known about an association between smoking and anophthalmia or microphthalmia. The interpretation of the results in the present study was

complex. There was no effect of maternal smoking on the total group of malformations but a study by Modéus et al. [15] indicated a "protective" effect for coloboma of the eye. As in many instances of microphthalmia the basic malformation is a non-closure of the chorioid fissure leading to coloboma, we removed cases with a stated coloboma and then the odds ratio for smoking increased. A further complication was the indicated association with maternal subfertility (women with fertility problems as an average smoke less than other women). After removal of cases whose mothers had reported involuntary childlessness, the odds ratio for smoking increased further and reached formal statistical significance. This observation needs to be confirmed or discarded by independent studies.

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Explanation of Figure

Figure 1: Graph showing rates per 10,000 births of anophthalmia and microphthalmia in Sweden, 1973-2001, based on data from four registers: Register of Congenital Malformations (1973-2001), Medical Birth Registry (1973-2001), Register of Visually Impaired Children (1981-2001), and Hospital Discharge Register (1987-2000). Graphs are based on moving 3-yearly averages.

Table 1: Summary of literature data on the prevalence at birth of anophthalmia or microphthalmia. Rates per 10,000 births.

		Anoph-		Microph-			
		thalmia		thalmia		Total	
Reference	Country	No.	Rate	No.	Rate	No.	Rate
Clementi et al. [2]	Italy	22	0.6	-	-	-	-
Stoll et al. [3]	France	6	0.2	36	1.7	42	1.9
Spagnolo et al. [4]	Italy	33	0.35	78	0.83	111	1.18
Källén et al. [5]	France	28	0.20	149	1.05	177	1.25
Källén et al. [5]	Sweden	59	0.27	142	0.65	201	0.92
Källén et al. [5]	USA	64	0.31	160	0.78	224	1.09
Bermejo et al. [6]	Spain	-	-	-	-	240	0.21
Busby et al. [7]	England	93	0.20	356	0.78	449	0.98

All data except for ref. 7 are from general congenital malformations registers, the English data are from a special register.

Table 2: Ophthalmologic characteristics of 78 children with bilateral anophthalmia or microphthalmia in the Register of Visually Impaired Children. Visual acuity represents binocular visual acuity.

	Total number	Visual acuity WHO category =0.3	1-2	3-5	unkown	No. with additional impairments
Anophthalmia	7	0	0	7	0	2
Microphthalmia						
primary diagnosis	38	1	8	22	7	17
secondary diagnosis	33	4	17	5	7	9

WHO category	Visual acuity
1	0.1-<0.3
2	0.05-<0.1
3	0.02-<0.05
4	light perception-<0.02
5	no light perception

Primary diagnosis: regarded as the dominant ophthalmic diagnosis

Secondary diagnosis: not the dominant ophthalmic diagnosis

Table 3: Maternal age and parity distribution of infants with anophthalmia or microphthalmia (cases) and of all infants (popul.). Odds ratios (OR) determined after adjustment for year of birth and parity in the analysis of maternal age and maternal age in the analysis of parity. Each group compared with all other groups.

	Number of infants			
	Cases	Popul.	OR	95%CI
Maternal age				
- 19	17	109071	1.35	0.71-2.58
20 - 24	68	682432	0.64	0.44-0.94
25 - 29	94	1082577	0.77	0.56-1.06
30 - 34	92	740301	1.39	1.01-1.92
35 - 39	51	273712	1.71	1.08-2.69
40 -	10	46972	1.78	0.65-4.88
Parity				
1	142	1232317	1.14	0.82-1.59
2	114	1060617	1.03	0.75-1.40
3	49	451435	0.80	0.52-1.22
4+	27	192518	0.95	0.52-1.72