

Compiling a national register of babies born with anophthalmia/microphthalmia in England 1988-94

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Abstract

Aim—To describe the prevalence of anophthalmia/microphthalmia in babies born in England 1988-94, as well as their overall survival, and the incidence of associated eye and non-eye malformations; to determine the usefulness of different sources of medical and health service information for establishing a retrospective register of anophthalmia/microphthalmia.

Methods—Multiple sources for initial (retrospective) case ascertainment were surveyed, followed by questionnaires to clinicians to establish severity, associated malformations, and aetiology for England, 1988-94. The population surveyed was all births in England for this time period (4 570 350 births). Cases included live births, stillbirths, or terminations after prenatal diagnosis of congenital anomaly, with anophthalmia/microphthalmia, with or without other malformations and syndromes. Trisomy 13 was subsequently excluded.

Results—The proportion of cases notified by any one information source was not more than 26% (Office for National Statistics Register 22%, paediatricians 26%, district sources 25%). Sixty nine per cent of cases (51% of severe cases) were notified by only one source. A total of 449 cases were reported, prevalence 1.0 per 10 000 births. The prevalence was stable over time, although the proportion notified by clinicians rose in more recent years. Thirty four per cent of affected babies had mild microphthalmia. Of those with severe anophthalmia/microphthalmia, 51% were bilateral, other eye malformations were present in 72%, non-eye malformations in 65%, and a "known aetiology" was attributed in 22%. Three quarters of those severely affected survived infancy.

Conclusions—Despite high response rates from the sources of information contacted, the lack of duplication between sources indicates the difficulties of retrospective ascertainment and the need for multiple sources when establishing a register. Anophthalmos/microphthalmos is usually associated with other malformations. Most cases are of unknown aetiology.

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Keywords: congenital malformation; anophthalmia; microphthalmia; register; epidemiology

A register has been established of all cases of anophthalmia/microphthalmia—absent or small eye(s)—born 1988-94 in England, as part of the National (English) Study of Geographical Variation and Clustering of Anophthalmia/Microphthalmia. This study was set up in response to public concern following media reports in early 1993¹ of alleged clusters of anophthalmia/microphthalmia in England, with a hypothesised link to exposure to the pesticide (fungicide) Benomyl.¹⁻² The time period of the register, covering about 4.5 million births, was chosen to overlap as far as possible with the period of concern, and to collect enough cases for geographical analysis, but not to go back so far as to risk severe under ascertainment of cases in earlier years.

The results of the geographical analysis have been reported separately.³ This study aims to present our experience of the usefulness of different sources of medical and health service information for establishing a retrospective register of anophthalmia/microphthalmia and the operational difficulties we encountered; and to describe the prevalence of anophthalmia/microphthalmia during this period, as well as the overall survival of children with this condition, and the incidence of associated eye and non-eye malformations.

Methods

The population surveyed included all births in England 1988-94 (4 570 350 live and stillbirths, and 4 538 790 live births). Cases included live births, stillbirths, or terminations following prenatal diagnosis of congenital anomaly.

The register was established as a two stage process, with data collection starting in 1994. Stage 1 involved accessing multiple sources of information for notification of cases, with minimal identification details including name, postcode, whether the child had anophthalmia or microphthalmia, and the names of clinicians involved in the care of the child. The sources accessed were: the Office for National Statistics (ONS) congenital malformation register (via notifying districts); regional registers (including the Northern Region and North Thames (West) registers of congenital anomalies, and the Oxford Region register of early childhood impairments); the Moorfields Hospital national database; district information sources (child health surveillance systems, special needs registers, etc., as indicated in answer to a letter to directors of public health); all paedia-

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tricians and ophthalmologists and all medical genetics and pathology departments; cytogenetics laboratories; the National Artificial Eye Service; and a parent support group. Children notified were flagged by the National Health Service Central Register who notified us of any deaths among them.

Stage 2 of the process involved sending a questionnaire to all clinicians indicated as being involved in the care of the child. The main aim of the questionnaire was to establish the severity of microphthalmia so that mild cases, whom it was expected might be variably reported, could be identified and excluded from geographical analyses. A definition of “mild” microphthalmia was determined as equivalent to a globe diameter (axial length) at birth of 15 mm or over—within 3 standard deviations of the mean globe diameter. Cases verified as anophthalmia, or severe to moderate microphthalmia, we refer to here as “severe.” The questionnaire included

questions on the estimated severity (mild, moderate, severe) with the aid of a photo sheet (fig 1), the measured and estimated global (axial) diameter, the corneal diameter, palpebral fissure length and visual function of each eye. For “severe” cases, a further aim of the questionnaire was to identify children with known aetiology—for example, family history, genetic syndromes or maternal infections—and to elicit information on laterality and other eye and non-eye malformations which could later be of use in creating subgroups of anophthalmia/microphthalmia for detailed analysis.

For ophthalmologists, who were contacted later than other clinicians, stages 1 and 2 were combined such that they were also sent at the same time questionnaires for children already notified in their care, as well as a request for notification of additional children.

Clinicians and indeed all sources contacted for stage 1 were asked to respond using prepaid

A Mild microphthalmia



B Moderate microphthalmia



C Severe microphthalmia



Figure 1 Examples of microphthalmia from the National Register.

Table 1 Response rate for stage 1 (percentage of persons contacted who responded*) and stage 2 (percentage of questionnaires completed†)

| Source of information | Total No contacted | Stage 1 | Stage 2 |
|--------------------------------------|--------------------|---------|---------|
| ONS Congenital Malformation Register | 276* | 78%* | |
| District Health Authority sources | 270 | 87% | |
| Ophthalmology | 718 | 76% | 73% |
| Paediatricians | 938 | 85% | 89% |
| Clinical genetics departments | 22 | 62% | 73% |

* For ONS, the figures given represents the number of anonymous SD56 notifications sent by ONS to the notifying districts and the percentage returned by the districts to the research team.

† This figure refers to the percentage for which a reply was received, excluding situations where a questionnaire was sent in error (4%), the child could not be traced in the hospital records (11%) or no reminders were sent because full data had already been obtained from other sources (17%).

envelopes as to whether they had seen cases. Reminders were sent for both stages 1 and 2 to increase the response rate. Three postal reminders and a telephone reminder were conducted at both stages for paediatricians and at the combined stages for ophthalmologists. One reminder was sent to genetics departments for stage 1, and three for stage 2. The ONS sent two reminders and a telephone reminder on our behalf to districts concerning cases on the ONS register for stage 1.

A full report of the method of access to different information sources and their response is available on request.

Trisomy 13 is the most common chromosomal syndrome associated with anophthalmia/microphthalmia. All cases of trisomy 13, with or without eye involvement, were initially requested for notification and follow up, but were excluded from this study.

Information on aetiology obtained in questionnaires on "severe" cases was reviewed by one of the authors (Robin Winter) to establish which cases were of "known aetiology."

The study was put before ethics committees, as appropriate. To preserve confidentiality names and addresses were not entered on the computer, and kept separately from all other clinical details in a locked cabinet. Names and addresses were required to prevent duplication

Key messages

- One in 10 000 babies born in England has anophthalmia or microphthalmia, one third of whom are mildly affected
- Most babies born with anophthalmia/microphthalmia have additional malformations
- Retrospective case ascertainment for conditions like anophthalmia/microphthalmia poses particular difficulties due to incomplete or inappropriate diagnostic indexing of existing data collection systems
- The ONS Congenital Malformation Scheme is very incomplete in its ascertainment of babies born with anophthalmia/microphthalmia, whether mild or severe
- Multiple sources of case ascertainment are indispensable for establishing a register of a condition such as anophthalmia/microphthalmia

of cases on the register, and to allow follow up with questionnaires to clinicians.

Results

STAGE 1 NOTIFICATIONS

The response rate from the various sources of notification is shown in table 1. A total of 490 possible cases were notified to the study. Sixty nine per cent were notified by only one source (fig 2). No one source identified more than 26% of cases nationally, with paediatricians, district sources, and the ONS congenital malformations register notifying the greatest proportion of cases. If any one source had not been notified, up to 11% of cases would not have been notified to the register (fig 2). The three regional registers combined knew of 52% of cases in their areas alone. The two registers covering the entire time period knew of 55% (Oxford Region) and 63% (Northern Region) of cases in their regions. The contribution of ophthalmologists shown in fig 2 is an underestimate, as they were not given the opportunity

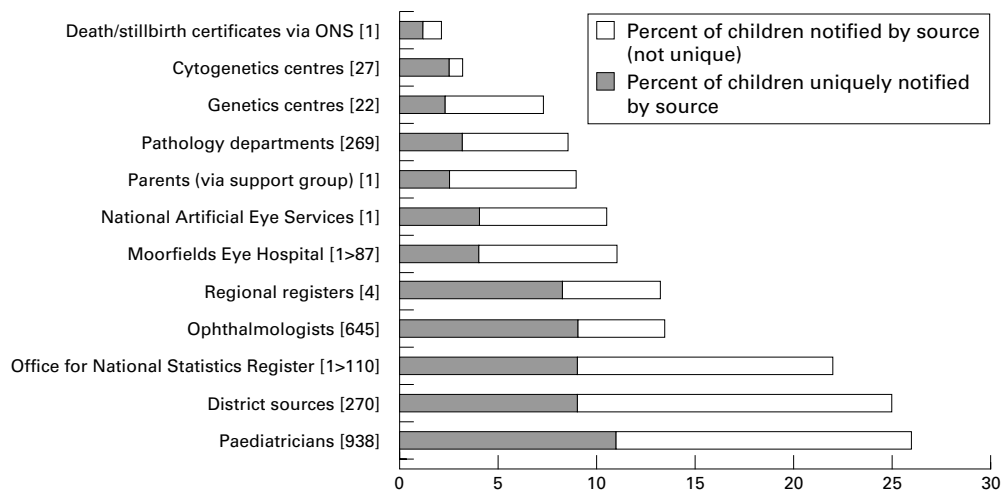


Figure 2 Notifications of anophthalmos/microphthalmos in England by source, with percentage uniquely notified.

independently to notify the 210 children already known to be in their care when they were first contacted.

"Severe" cases were more likely to be multiply notified, with 51% notified by only one source compared with 80% of mild cases. Correspondingly, individual sources notified higher proportions of "severe" cases: paediatricians 38%, the ONS register 29%, and district sources 25%. Conversely, the proportion of mild cases (out of cases with known severity) among ONS notifications was only 10%, compared with 23% of those notified by paediatricians, 35% from regional registers, and 36% from district sources.

"Severe" cases surviving infancy were particularly likely to be multiply notified: 43% were notified by one source alone. The proportion of cases who survived infancy was least among ONS notifications (55%) compared with 63% of those notified by regional registers and 80% of those notified by paediatricians.

STAGE 2 QUESTIONNAIRE RESPONSE RATES

Of the 490 notified cases, 77% of children had at least one and 36% more than one questionnaire returned by clinicians. Response rates for each clinician specialty are shown in table 1. One hundred and twelve children did not have a completed questionnaire either because no clinician was known (55 cases including 39 anonymously notified cases), or no clinician returned a questionnaire (57 cases).

VERIFICATION OF CASE STATUS AND SEVERITY

From the information obtained from questionnaires, and occasionally further notification information, 41 cases (8%) were excluded as not having an/microphthalmos. These cases had either no eye defect (16 cases), acquired anophthalmos secondary to trauma or another condition (4 cases), or an eye condition that was not a congenital anomaly such as retinopathy of prematurity (5 cases) and retinoblastoma (4 cases). A further five cases were notified with holoprosencephaly and cyclops, an essentially different condition, but these remain in the figures, except where indicated.

Table 2 shows the distribution of severity among the remaining 449 cases. Thirty four per cent of children for whom severity could be judged had mild microphthalmos. In most microphthalmos cases estimation of severity was based on clinical judgment as no measurements were available (5% had ultrasound measurement, 25% corneal diameters including 8% where this was estimated rather than measured, 8% palpebral fissure lengths and 55% visual function). In 45% of cases where more than one clinician had provided information on microphthalmos severity, there was some disagreement, but in only half of these cases did the disagreement concern whether microphthalmos was mild or "severe." These disagreements (mild or not) could generally be resolved on a case by case basis by giving priority to ophthalmologist judgments and measurements, or by looking at other supporting information.

Table 2 Number of cases by severity of anophthalmos/microphthalmos

| | |
|--------------------|-----|
| Anophthalmos | |
| Confirmed | 76 |
| Unconfirmed* | 17 |
| Microphthalmos | |
| Severe to moderate | 149 |
| Mild | 113 |
| Unknown severity | 94 |
| Total | 449 |

* These cases were notified as having anophthalmos, but no questionnaire was received in confirmation.

Table 3 Number of cases and "severe" cases by survival status, laterality, and presence or absence of other eye or non-eye malformations

| | All cases | % | Confirmed "severe" cases | % |
|---------------------------------|-----------|-----|--------------------------|-----|
| Total | 449 | 100 | 221 | 100 |
| <i>Survival status:</i> | | | | |
| Surviving 1997 | 311 | 69 | 165 | 75 |
| Liveborn, died | 69 | 15 | 36 | 16 |
| Liveborn, survival unknown | 22 | 5 | 2 | 1 |
| Stillbirth | 19 | 4 | 9 | 4 |
| Termination of pregnancy | 22 | 5 | 8 | 4 |
| Unknown | 6 | 1 | 1 | 0 |
| <i>Laterality:</i> | | | | |
| Unilateral | 237 | 53 | 109 | 49 |
| Bilateral | 158 | 35 | 112 | 51 |
| Unknown | 54 | 12 | 0 | 0 |
| <i>Other eye malformations:</i> | | | | |
| Present | 281 | 63 | 142 | 64 |
| Absent | 65 | 14 | 55 | 25 |
| Unknown | 103 | 23 | 24 | 11 |
| <i>Non-eye malformations:</i> | | | | |
| Present | 249 | 55 | 143 | 65 |
| Absent | 110 | 24 | 78 | 35 |
| Unknown | 90 | 20 | 0 | 0 |

SURVIVAL, LATERALITY AND PRESENCE OF OTHER EYE AND NON-EYE MALFORMATIONS OR SYNDROMES

Sixty nine per cent of all cases (table 3) were still alive in 1997. Children with "severe" anophthalmia/microphthalmia were less likely to survive (75%) than children with mild forms (88%). Children for whom severity was unknown were more likely to have died (43%) or be of unknown survival status (22%). Most deaths of live born cases (89%) were in the first year of life, and four fifths of these were in the neonatal period. Multiply malformed children were less likely to survive (57%) than children with only eye malformations (99%).

An/microphthalmia was bilateral in 51% of "severe" cases (table 3), but in only 29% of mild cases.

Other eye malformations were present in 72% of severe cases for whom the information was known (table 3), most commonly coloboma (42% of those with other eye malformations) and cataract (21%), with similar proportions among mild cases. Persistent hyperplastic primary vitreous was the next most common associated eye condition overall, but associated mainly with mild microphthalmia (18%) and not "severe" an/microphthalmia (4%).

Non-eye malformations and syndromes were present in 65% of "severe" cases (table 3). A wide range of malformations were associated with severe anophthalmos/microphthalmos. Musculoskeletal anomalies of the skull, face, and neck were particularly common (24%), as were ear anomalies (17%), facial clefts (15%) and hydrocephaly (10%).

A "known aetiology" was attributed in 22% of "severe" cases, including syndromes of genetic origin, a family history strongly suggestive of genetic origin, bilateral cases with parental consanguinity, and cases of established maternal infection.

PREVALENCE

The total of 449 registered cases gave a prevalence of 1.0 per 10 000 live and stillbirths (95% CI 0.9–1.1). The prevalence of "severe"an/

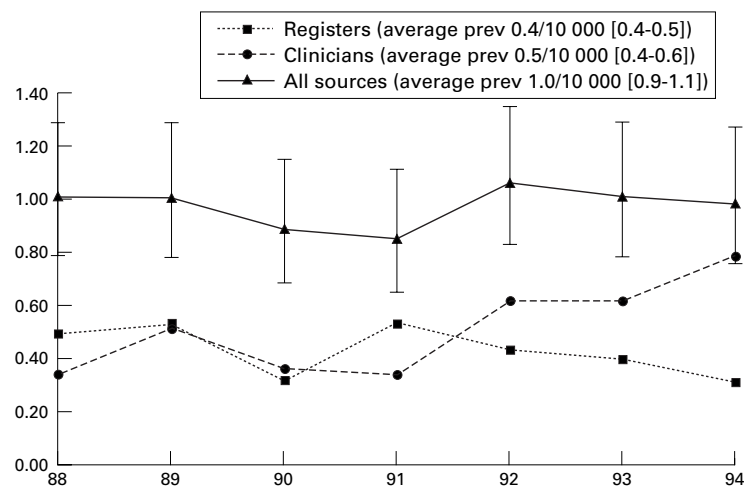


Figure 3 Anophthalmos/microphthalmos prevalence by year of birth: notification from clinicians vs register.

microphthalmos is estimated at 0.65 per 10 000 (95% CI 0.56–0.74). This prevalence assumes that the proportion of mild cases would be the same among cases of known and unknown severity. Although more cases of unknown severity had died and were thus less likely to be mild, taking into account survival status only changes the prevalence estimate to 0.66 per 10 000. The live birth prevalence rate was 0.89 per 10 000 (95% CI 0.80–0.98) for all cases and 0.57 per 10 000 (95% CI 0.50–0.64) for “severe” cases.

The prevalence was stable over time (fig 3) (χ^2 for trend, $p=0.86$), as was the estimated prevalence of “severe” cases (χ^2 for trend, $p=0.41$). The prevalence of cases notified by clinicians rose significantly over time (χ^2 for trend, $p < 0.01$) until 1994 when the clinician based estimate was 80% of the total estimate, but registers and databases notified a fairly stable prevalence (χ^2 for trend, $p=0.11$) (fig 3).

Discussion

Little is known of the aetiology of most cases of an/microphthalmia. It is a component of a vast range of genetic syndromes,⁴ but which, other than trisomy 13, account for only a small proportion of cases.⁵ The best established environmental causes in people are certain maternal infections such as rubella, toxoplasmosis, and cytomegalovirus, but these also are diagnosed in only a small proportion of cases.^{5,6} Among “severe” cases on our register, a “known aetiology” could be attributed only in 22%. There is strong evidence for maternal hyperthermia being a cause in people,^{6,7} and microphthalmia is part of the fetal alcohol syndrome spectrum of anomalies.⁶ Furthermore, a variety of maternal exposures, including thalidomide, isotretinoin, toluene abuse and insecticides, have been reported to be associated with microphthalmos.^{6,8,9} In animal experiments a wide range of chemical exposures result in an/microphthalmia,⁶ often associated with other anomalies, including the fungicide Benomyl¹⁰ which sparked some of the original concern about clusters and their causes. However, animal experimental doses tend to be very high compared with human exposures and the

main interest of these data may be in suggesting the lack of specificity of an/microphthalmia as an outcome of any one exposure. As our data confirm, an/microphthalmia is a rare congenital anomaly, usually associated with other congenital anomalies in the same child. It may therefore result from a variety of different exposures, alone or in combination, but that a high exposure dose or a background of genetic or environmental susceptibility is needed for an/microphthalmia to manifest, and this would usually lead to abnormal development of other organs as well.

We estimate a prevalence of an/microphthalmia of 1 per 10 000 births in England, of which one third of cases can be classified as mild. We can make some estimation of the potential under ascertainment of cases of an/microphthalmia in this study by external and internal comparison. First, two international studies (collaborations between prospective congenital anomaly registers) reported a total prevalence of non-chromosomal an/microphthalmia of 1.3 per 10 000¹¹ and 1.2 per 10 000,⁵ although these figures were averages over significantly varying prevalences between registries. These figures correspond more closely with the prevalence found in the three regions of England which had prospective registers (1.18 per 10 000) compared with all other regions (0.94 per 10 000). However, it should be noted that these three registers had registered only 52% of the total cases found in their regions, and it is likely that all registers across the world are incomplete, but to different extents. Second, the complete identification and exclusion of trisomy 13 among cases can also have marked effects on prevalence rates, because, when included, they can account for one quarter of all cases.⁵ Third, our very low duplicate notification rate leads us to suspect that some cases must be missing. The higher duplicate notifications among “severe” cases probably indicates a better ascertainment of “severe” cases. On the other hand, children who had died were probably selectively under ascertained, and this is supported by the lower survival rate in the two regions with prospective congenital anomaly registers (51%) compared with the regions without such registers (74%). Overall, we believe that about 15–20% of cases may be missing, particularly mild and “severe” cases who died during infancy.

We obtained a relatively high response from all clinicians and other sources of information contacted. Nevertheless, no source identified more than one quarter of cases. This emphasises the crucial use of multiple sources of information for the establishment of a register, even when it is known that one source potentially “knows of” a very high percentage of cases. For example, of 312 ophthalmologists replying that they had no cases, 44 (14%) did have cases notified by another source as being under their care. By the end of the study, we had identified an ophthalmologist for 72% and a paediatrician for 79% of children on the register. In the absence of information systems with the possibility of diagnostic retrieval, clinicians mainly had to rely on their memory,

and this is clearly shown by the doubling of the prevalence of notified cases between 1988 and 1994. In 1994, around four fifths of cases were notified by clinicians, and it is clear that any study wishing to rely on clinician notification alone must do so in a prospective manner, like, for example, the British Paediatric Surveillance Unit.¹² However, this poses obvious time constraints in responding to issues of public concern, as our seven years of data would have taken seven years to collect.

Registers and sources of data other than clinicians could only identify half of all cases eventually registered. The ONS congenital malformation register in particular identified 22% of all cases and 29% of "severe" cases. Deficiencies in ONS data have been discussed elsewhere¹³ and some restructuring is currently taking place,¹³ but single condition or regional registers will be vital to audit the success of these changes. The Hospital Episode System (HES) is at present not designed to allow researchers to identify cases and follow them up, and its completeness for congenital anomalies has never been fully evaluated. An initial look at anonymous cases recorded by HES suggests a low degree of overlap with our register, and this observation requires further investigation.

The ultimate objective of any research provoked by cluster concerns must be to advance knowledge about the aetiology of an/microphthalmia and through this, probably of other congenital anomalies. The usefulness of establishing a register for answering public concern about clusters will become apparent when the register has been fully exploited, for geographical clustering analysis,³ for further

ecological and case control studies, and for a detailed review of clinical characteristics of cases, currently underway.

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