Trends over time in the incidence of congenital anophthalmia, microphthalmia and orbital malformation in England: database study

Author: Aruna Dharmasena [1, 2]

Tiarnan Keenan[2]

Raph Goldacre[3]

Nick Hall [3]

Michael J Goldacre[3]

Institution:

1. Manchester Royal Eye Hospital, Oxford Road, Manchester M13 9WH, United Kingdom
2. Moorfields Eye Hospital, 162 City Road, London EC1V 2PD, United Kingdom
3. Unit of Health-Care Epidemiology, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom

Corresponding Author:

Name: Aruna Dharmasena

Address: Adnexal Service, Moorfields Eye Hospital,

162 City Road, London EC1V 2PD, United Kingdom

Telephone: +44(0) 784 6158964

e-mail: aruna_dharmasena@hotmail.co.uk

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Abstract

Aims

To study trends over time in the incidence of congenital anophthalmia, microphthalmia, and orbital malformations in England, along with changes in hospital admission rates for these conditions.

Methods

Using English national hospital episode statistics, the annual rate of hospital admissions related to anophthalmia (1990-2011), microphthalmia (1990-2011) and congenital malformations of orbit/ of lacrimal apparatus (1999-2011) were calculated per 100,000 infants. The records were person-linked from 1999 to 2011, which enabled annual person-based 'first record' rates to be calculated as proxies for incidence.

Results

The annual incidence of congenital anophthalmia remained stable in England over the period 1999-2011 at approximately 1.5 (95% CI 1.2-1.8) cases per 100,000 infants. The annual incidence of congenital microphthalmia increased modestly in recent years, for example from 5.9 (95% CI 3.9-7.8) cases per 100,000 infants in 2004 to 11.4 (95% CI 8.9-14.0) in 2010. The annual incidence of hospitalised congenital orbital/lacrimal malformations remained steady over the study period.

Counting multiple admissions per person, annual admission rates for anophthalmia fluctuated but generally remained stable. They doubled for microphthalmia from 11.0 (95% CI 8.4-13.5) admissions per 100,000 infants

in 1990 to 22.1 (95% CI 17.7-24.6) in 2011. They showed a small non-significant increase for orbital/lacrimal malformations.

Conclusion

The incidence of congenital anophthalmia has remained stable in England in recent years, as has that of congenital orbital/lacrimal malformations, while the incidence of microphthalmia has increased modestly. Hospital admission rates for this group of conditions increased over time. These data may be useful for planning service provision.

231 words

Introduction

Anophthalmia and microphthalmia are rare congenital conditions defined respectively by the absence of an eye or the presence of a small, poorly developed eye within the orbit. Together with congenital malformations of the orbit and ocular adnexa, these conditions may present substantial challenges to the ophthalmologist and orbital surgeon, and a significant treatment burden to the patient and family.

Anophthalmia and microphthalmia are thought to represent a phenotypic spectrum (1), (2). While their exact pathogenesis is not fully understood, genetic causes can include chromosomal abnormalities (together with some monogenic and polygenic variants), while environmental factors such as intrauterine infections or toxins may also be involved (2). These factors lead to abnormal differentiation of the neuroectodermal tissues required for ocular and adnexal development, such that one or both eyes fail to develop normally, with a variable degree of abnormalities ranging from microphthalmia to ‘true anophthalmia’ (1), (2). In one third of cases, the ocular pathology is associated with a systemic syndrome (2).

Individuals with these conditions usually have a high degree of visual impairment, including bilateral blindness in some cases; together with the altered physical appearance, this may have substantial implications on the social and psychological welfare of the child and family (3). Since normal facial development is highly dependent on orbital growth, the timely management of severe microphthalmic and anophthalmic orbits is

fundamental in preventing gross facial disfigurement. Serial conformers and socket expanders are often required in these individuals, but additional measures may be required in some cases, particularly in the presence of associated eyelid abnormalities. In general, affected individuals will require multiple hospital admissions and operations over many years, and will likely remain under the care of the oculoplastic surgeon, orbital surgeon and ocularist for much of their life.

While anecdotal reports have suggested that hospital admissions related to ocular and adnexal malformations have been increasing in England in recent years, we are not aware of any published literature in this area. We have therefore used linked English national Hospital Episode Statistics (HES) to analyse annual hospital admission rates for anophthalmia, microphthalmia, and congenital malformations of the orbit/adnexa from 1990 to 2011.

Methods

Since 1990, every day-case and inpatient admission in English National Health Service (NHS) hospitals has been recorded, as a statistical summary of the case, in HES. A day case, in the English NHS, is a planned hospital admission in which the patient is not intended to stay overnight. Records of babies born in hospital, as well as records of day case and inpatient care, were included in the study to capture diagnoses made in infants when still in hospital after birth and who were, technically, not ‘admissions’. In this study, we analysed HES statistics relating to anophthalmia and microphthalmia from

1990 to 2011, and HES statistics relating to congenital malformations of orbit/agenesis of lacrimal apparatus from 1999 to 2011 (data pre-1999 not available, see below). The HES data were provided by the English national Health and Social Care Information Centre (HSCIC). HSCIC was unable to provide data from 2012 onwards. Records of day-case care and inpatient admissions were identified for these congenital malformations using the codes of the International Classification of Diseases (ICD). The codes used for anophthalmia were 743.0 in ICD-9 (up to 1995) and Q11.0-Q11.1 in ICD-10 (from 1995 onwards). The codes used for microphthalmia were 743.1 in ICD-9 and Q11.2 in ICD-10. Those used for congenital malformations of orbit and agenesis of lacrimal apparatus were Q10.7 and Q10.4 in ICD-10; they were not separately identifiable in earlier revisions (being grouped together with other congenital anomalies such as intraocular malformations).

The HSCIC data provided to our research team included encrypted values of unique identifiers for each individual on each HES record: these were based on the NHS number (unique to each person registered for NHS care) and the HES Identification Number (unique to each person using NHS hospital care). Record linkage was used to determine the incidence, as closely as possible, of the malformations. Record linkage means that the anonymised records for each individual can be traced over time through multiple admissions, such that one can distinguish numbers of admissions from numbers of separate individuals being admitted. Linkage of England HES data only became possible from 1999. Using the record-linked datasets, two annual rates were generated as follows: the episode-based rate includes all episodes of

admission, regardless of how many admissions an individual has (the "hospital admission rate"); the person-based 'first record' rate counts each person once, and once only, and allocates the person to the year in which the first-recorded admission occurred (the "incidence rate"). English national population denominators were obtained from the Office for National Statistics for each calendar year. The analyses were confined to children less than one year of age to approximate the birth incidence of the malformations.

Results

Congenital anophthalmia

Incidence rates

The annual incidence of anophthalmia fluctuated from year to year, with no strong evidence of an overall rise or fall (Figure1). The lowest recorded annual incidence was 0.4 (95% confidence interval, 0.0 to 1.3) per 100,000 infants, based on 3 infants out of a total of 679,100 infants in 2011. The highest recorded annual incidence was 2.4 (1.3 to 4.0), based on 14 infants out of 592,200 in 1999. The data did demonstrate some significant differences in incidence rates between years: for example, the rate of 2.3 per 100,000 infants in 2005 was outside the upper 95% confidence interval of 1.3 in 2011. However, no systematic and significant trend was observed overall.

Considered as grouped rates, to bolster statistical power, the annual rates for both sexes combined in 1997-2001, 2002-2006 and 2007-2011 were, respectively: 1.6 (1.0 to 2.2) per 100,000 infants, 1.5 (1.0 to 1.9) and 1.4 (1.0 to 1.8). The corresponding rates for females were 1.9 (1.0 to 2.8), 1.4 (0.8 to

2.0) and 1.0 (0.5 to 1.5). Those for males were 1.4 (0.6 to 2.1), 1.6 (1.0 to 2.2) and 1.8 (1.2 to 2.5). Thus, the data suggest, though rather weakly, that incidence rates in recent years may have increased for males but decreased for females.

Hospital admission rates

Similar trends were observed over time for annual rates of hospital admissions for anophthalmia (Figure 1), i.e. annual fluctuations but no strong evidence of an overall increase or decrease over time. The grouped rates for both sexes combined in 1997-2001, 2002-2006 and 2007-2011, respectively, were 2.8 (1.7 to 3.9), 5.0 (3.9 to 6.1) and 4.1 (3.1 to 5.1).

Congenital microphthalmia

Incidence rates

The annual incidence of microphthalmia was substantially higher than that for anophthalmia, for example 10.0 versus 0.4 per 100,000 infants in 2011. The incidence of microphthalmia remained relatively stable going from 10.8 (8.2 to 13.5) per 100,000 infants in 1999 to 10.0 (7.6 to 12.4) in 2011 (Figure 2).

In contrast to the sex-specific trends observed for anophthalmia, the pattern for microphalmia was similar in both sexes.

Hospital admission rates

Compared to annual incidence rates, annual admission rates for microphthalmia showed a steeper increase over time, from 11.0 (8.4 to 13.5) admissions per 100,000 infants in 1990 to 22.1 (18.6 to 25.6) in 2011 (Figure

2), i.e. increasing divergence between incidence and admission rates, attributable to an increase in multiple admissions per person with microphthalmia.

Congenital malformation of orbit / agenesis of lacrimal apparatus

Incidence rates

Annual incidence rates of these congenital malformations fluctuated from year to year but generally demonstrated a small and non-significant increase over the study period, from 0.5 (0.0 to 1.1) per 100,000 infants in 1999 to 0.7 (0.1 to 1.4) in 2011 (Figure 3). No important differences were observed between trends in males and females.

Hospital admission rates

Annual rates of hospital admissions related to these malformations generally followed annual incidence rates closely, i.e. fluctuated from year to year but generally demonstrated only a small increase over the study period.

Discussion

Congenital anophthalmia and microphthalmia are rare but severe conditions, where each affected individual will require extensive care from ophthalmology and orbital services over many years, together with social and psychological support.

Our results show that the incidence of anophthalmia has remained stable in England over the past decade. The mean annual incidence has been 1.5

cases per 100,000 infants over the study period, representing an average of 9 infants newly diagnosed per year. The annual incidence of microphthalmia has been much higher at an average of 8.6 cases per 100,000 infants (representing around 53 infants newly diagnosed per year); our results also show some evidence of a small increase in incidence rates in recent years. By comparison, the incidence of congenital orbital/lacrimal malformations is much lower, with an annual rate of 0.5 cases per 100,000 infants (representing 3 infants newly diagnosed each year). For microphthalmia, the annual rate of hospital admissions doubled from 1990 to 2011, representing an increase from 71 admissions in 1990 to 150 in 2011.

Potential factors affecting the incidence of these congenital conditions include both genetic and environmental factors (1), (2). Genetic factors include chromosomal abnormalities (such as duplications, deletions and translocations, e.g. duplication 3q syndrome), monogenic causes (particularly in *SOX2*) and polygenic variants (in genes including *PAX6*, *OTX2* and *CHX10*) (2). Potential environmental factors include gestational infections (e.g. rubella and toxoplasmosis), vitamin A deficiency, and other exposures (e.g. fever, hyperthermia, X-rays and toxic drugs such as alcohol and warfarin) (2). Because of the complex balance of potential causative factors, it is difficult to know exactly why incidence rates for anophthalmia and microphthalmia may be stable or increasing, respectively. One would assume that the incidence of congenital infections and other toxic insults has been decreasing in England in recent years (4), (5). However these factors might potentially be balanced by other effects such as improved care and survival

for children with major systemic abnormalities (i.e. those associated with anophthalmia/microphthalmia) and changes in the prevalence of genetic disorders (e.g. through altered rates of consanguinity). Other factors potentially affecting the measured incidence may include increased rates of pre-natal diagnosis leading to termination of pregnancy, decreased threshold for hospital admission (e.g. for imaging studies or surgical treatment), and changes in accuracy of diagnosis and coding (e.g. better discrimination between microphthalmia and anophthalmia).

The increase in the annual number and rate of hospital admissions for microphthalmia is likely to be explained by an increased understanding of the fact that steady growth of the orbit is crucial for development of the mid-face. This is usually achieved by techniques including serial insertion of custom-made confirmers and injection of orbital expanders. Together with ocular and orbital imaging procedures, these interventions may require general anaesthesia and day case or inpatient admissions. These data are useful in the planning of services for the future, particularly in specialist centres where much of this work is undertaken.

Previous studies

There is a paucity of epidemiologic information on severe congenital malformations of the eye, orbit and ocular adnexa. Epidemiologic studies of this kind are difficult to conduct because of the rarity of these conditions and, to the best of our knowledge, there are no studies examining time trends in the English population over the past two decades. Previous published studies

have generally used data extracted from national congenital anomaly registers (6) (7), (8), (9). In previous studies carried out on predominantly Caucasian populations, the incidence of anophthalmia has been reported between 0.6 and 6 cases per 100,000 births (6), (10), (11), (12), (13), (14), (15), (16), while that of microphthalmia has reportedly ranged from 5.5 to 17.0 per 100,000 births (6), (10), (11), (12), (13), (14), (15), (16). Our incidence figures sit within these ranges at 1.7 and 7.7 cases per 100,000, respectively.

The study most comparable to ours was undertaken by the Surveillance of Eye Anomalies UK (SEA-UK) Special Interest Group over a period of 18 months, from October 2006, throughout the United Kingdom (6). For anophthalmia, the incidence figure reported in this study was 0.6 (0.3 to 1.3) per 100,000, based on 7 cases reported over the 18 month study period (6), equivalent to fewer than 5 cases per year. By comparison, the incidence rates in our study during the calendar years 2006, 2007 and 2008 were more than twice that, despite our study being limited to England only. The equivalent numbers of cases captured in our study for England only during the calendar years 2006, 2007 and 2008 were 13, 8 and 15, respectively.

The same investigators reported an incidence for microphthalmia (isolated and colobomatous) of 5.5 (3.8 to 7.8) per 100,000, based on 63 cases reported over the 18 month study, equivalent to 42 cases per year (4). By comparison, the incidence figures in our study during the calendar years 2006, 2007 and 2008 were 8.0, 7.6 and 9.3 cases per 100,000, respectively, i.e. somewhat higher in our study, again despite our study being limited to

England only. The equivalent numbers of cases captured in our study during the calendar years 2006, 2007 and 2008 were 49, 49 and 62, respectively.

These discrepancies may perhaps be explained partly by under-reporting of relevant cases to the British Ophthalmic Surveillance Unit in the previous study (6), though we can not exclude the possibility of over-ascertainment in our study through inaccurate diagnosis or coding. In particular, we can not exclude the possibility that some cases of microphthalmia could have been coded incorrectly as anophthalmia (hence leading to increased numbers in our study), especially since these conditions are thought to exist on a spectrum.

We are not aware of any previous studies examining the incidence of congenital abnormalities of the orbit or agenesis of the lacrimal system.

Strengths and weaknesses

The main strengths of this study include the use of a dataset that covers the whole of the English NHS population and has existed over a long time span. Linkage in the dataset means that we have been able to distinguish between number of hospital admissions and number of separate infants being admitted. We have therefore provided incidence rates of these congenital anomalies as well as incidence rates of hospital admissions. It is likely that every case of these congenital anomalies will have been recorded in hospital statistical data, either because the baby was born in hospital or because, if not born in hospital, is likely to have been admitted after birth. Our findings are consistent

with those from studies conducted in other European countries. However, potential weaknesses in the dataset include lack of evidence about the accuracy of diagnostic coding and the exclusion of admissions to hospitals in the private sector; privacy regulations in England preclude access to original case records in studies like ours. In addition, data capture in this study is dependent on hospital admission. This means that individuals will not be captured in cases where no hospital admission occurs for imaging, surgery or medical reasons, e.g. mild microphthalmia where no orbital imaging or surgical intervention takes place.

In conclusion, our results show that the incidence of congenital anophthalmia has remained stable in England over the past decade at between about 1 and 2 cases per 100,000 live births. The incidence is higher than previous UK estimates but at the lower end of the range reported previously for various European countries. In addition, we have demonstrated that the incidence of congenital microphthalmia has increased modestly in England over the past decade, again towards the lower end of the range reported in previous European studies. This has been accompanied by a larger rise in the rate of hospital admissions for microphthalmia, representing an increase in the number of multiple admissions per child (i.e. for imaging and surgical procedures). These data may provide insights into potential causative factors; for example, incidence rates for these congenital abnormalities are not decreasing despite declining rates of congenital infections and other improvements in antenatal care. This information is also helpful for planning service provision in this area, as children with anophthlamia/microphthalmia

require extensive care from ophthalmology and orbital departments over many years.

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Conflicts of interest

None to declare.

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Contributorship statement

AD had the idea for the paper. NH and MJG were responsible for the data acquisition. MJG designed the analyses. NH and RG analysed the data. All authors interpreted the data, and wrote and revised the paper. MJG is guarantor.

Ethical approval

Ethical approval for analysis of the record linkage study data was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee.

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Figure legends

Figure 1. The incidence of congenital anophthalmos and annual incidence of congenital anophthalmos related hospital admissions in England (1990 – 2011).

Figure 2. The incidence of congenital microphthalmos and annual incidence of microphthalmos related hospital admissions in England (1990 – 2011).

Figure 3. The incidence of congenital malformations of orbit and agenesis of lacrimal apparatus and the incidence hospital admissions related to these congenital anomalies in England (1998 – 2011).