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Haralambous, E; Weiss, HA; Radalowicz, A; Hibberd, ML; Booy, R; Levin, M (2003) Sibling familial risk ratio of meningococcal disease in UK Caucasians. *Epidemiology and infection*, 130 (3). pp. 413-8. ISSN 0950-2688

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Sibling familial risk ratio of meningococcal disease in UK Caucasians

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(Accepted 30 January 2003)

SUMMARY

To quantify the host genetic component of meningococcal disease (MD) susceptibility, the sibling risk ratio (λ_s) was calculated as the ratio of observed MD cases among 845 siblings of 443 UK Caucasian cases to that expected, calculated from age-calendar year specific rates for England and Wales. Twenty-seven siblings contracted MD compared with an expected 0·89, generating a λ_s value of 30·3. Overestimation of λ_s due to *Neisseria meningitidis* exposure was minimized by excluding siblings with MD onset within set time points of the index case. Irrespective of whether siblings contracted MD more than 1, 3, 6, 9 or 12 months after the index case, the λ_s varied slightly (λ_s range: 8·2–11·9), suggesting that host genetic factors may contribute approximately one third of the total λ_s . Social class distribution did not differ between MD cases and the general population of England and Wales. This study is the first to calculate λ_s for MD and establishes that susceptibility to MD has a significant host genetic component.

INTRODUCTION

The importance of the host genetic contribution to infectious disease susceptibility is clearly illustrated by a greater than fivefold increased risk of dying from an infective disease in adoptees if a biological parent had died prematurely of infection. This compares to no significant increase in risk associated with the infectious death of an adoptive parent [1]. A significant genetic component to infectious diseases is also indicated by twin studies of tuberculosis [2], leprosy [3], malaria [4] and *Helicobacter pylori* infection [5] as well as the many positive associations between diseases and specific candidate host gene polymorphisms [6, 7].

Neisseria meningitidis is a commensal and pathogen in the human nasopharynx and is carried asymptotically by approximately 10–15% of the human population in open communities [8, 9]. Invasive disease occurs occasionally. Though a number of studies indicate that host genetics are important in the susceptibility to meningococcal disease (MD) [10–13], the relative contribution of host genetics to this susceptibility has not been quantified.

The sibling risk ratio of disease, λ_s , is a standard parameter used in genetic analysis to indicate the increased risk of disease in siblings of affected cases compared with the risk of disease in the general population. An increased risk of disease in siblings indicates a host genetic component to susceptibility. Unbiased estimates of λ_s are generally difficult to

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calculate for infectious diseases for two reasons: 1) estimates of λ_s for infectious diseases tend to overestimate the importance of the host genetics because of the increased risk of exposure to infection in family members compared with the general population, and 2) the risk of disease in the general population is generally not known accurately and may vary with age and calendar year.

In order to take into account the effect of exposure to *N. meningitidis* in siblings of affected cases, the duration between onset of MD in each affected case/affected sibling(s) pair was also taken into account. The time between *N. meningitidis* acquisition and invasive MD is unknown. Invasive MD is thought to occur within a few days of pharyngeal acquisition [14–17] as shown by individuals who contracted MD having acquired the organism within a week of MD onset. However, in two prospective studies where swabs were taken periodically, it was suggested that *N. meningitidis* may be carried for longer with acquisition occurring approximately 2 weeks [18] and 7 weeks [19] prior to onset of invasive MD. To minimize the effect of increased exposure to *N. meningitidis* and thus not overestimate the genetic effect, λ_s was calculated using a number of time cut-offs between the onset of MD in the affected case and the affected sibling(s) pair. The time cut-offs used were more than 1 week, 1, 3, 6, 9 and 12 months.

Age and calendar year-specific rates of MD were used to estimate the number of cases of MD to be expected by chance among the siblings of affected cases.

METHODS

Information ascertainment

Family information

Between the years 1995 and 2001, a questionnaire was sent to MD cases located throughout the UK from two sources: either members of the Meningitis Research Foundation (MRF) or children admitted to the Paediatric Intensive Care Unit (PICU) at St Mary's Hospital, Paddington, London. In cases admitted to PICU, MD diagnosis was confirmed by one or more of the following: isolation of meningococci from blood or CSF, detection of rising meningococcal antibodies or PCR detection of meningococcal genome in blood or CSF. In patients with no microbiological confirmation (approximately 13%), MD was diagnosed clinically when the patient presented with a petechial or purpuric rash and fever and features of

systemic sepsis or meningitis where no other pathogen was isolated despite extensive bacteriological and virological investigation. Cases recruited via the MRF had their MD diagnosis confirmed by the local hospital consultant.

In the questionnaire we sought information on the number of siblings in each family, their dates of birth, other affected family members, and dates of all MD onsets.

Notifications of meningococcal disease

The Public Health Laboratory Service (PHLS) supplied data on the number of notifications of meningococcal meningitis and meningococcal septicaemia for England and Wales for the periods 1974–2000 and 1989–2000 respectively. From 1982–2000, data were available for yearly age groups (0–97 and ≥ 98). From 1974–81, data were available for yearly ages 0–4 and then in the following groupings: ages 5–9, 10–14, 15–24 and ≥ 25 .

Population data

The Office for National Statistics (ONS) supplied population data for England and Wales for 1974–2000 by age (0–89 and ≥ 90).

Calculation of λ_s

Calculation of incidence data

For each year (1974–2000) the age specific risk of disease was calculated using the data supplied by the PHLS and the ONS. These data were used to calculate the cumulative risk of MD for each sibling of each MD case at the time of data ascertainment and their year of birth. For example, if a questionnaire was completed in 1999, the risk of disease for an individual born in 1995 was calculated as the sum of the risks of MD at age 0 in 1995, age 1 in 1996, age 2 in 1997, age 3 in 1998 and age 4 in 1999. The total risk of MD in all siblings of affected cases was the sum of these individual risks. The risk for 1974 was used to estimate risk for all previous years as notifications of MD were either not available or were not considered accurate prior to this date by the PHLS. The incidence rate for 1974 was no different to that for the following individual 10 years. The risk for 2000 was used to estimate risk for 2001, as data for 2001 were incomplete at time of analysis. With the introduction of the meningococcal C vaccine, the numbers of cases

Table 1. Sibling risk ratio by interval between onset of index case and sibling case

| Interval between MD onsets in index case and affected sibling(s) pairs | Number of affected siblings to index cases | Expected number of affected siblings | λ_s (95% CI) |
|--|--|--------------------------------------|----------------------|
| All data | 27 | 0.892 | 30.3 (20.0–44.0) |
| > 1 week | 16 | 0.878 | 18.2 (10.4–30.0) |
| > 1 month | 10 | 0.842 | 11.9 (5.7–21.8) |
| > 3 months | 9 | 0.859 | 10.5 (4.8–19.9) |
| > 6 months | 9 | 0.859 | 10.5 (4.8–19.9) |
| > 9 months | 8 | 0.854 | 9.4 (4.0–18.5) |
| > 12 months | 7 | 0.822 | 8.2 (3.4–17.9) |

in 2001 were less than for 2000. This, however, only generated a slightly higher incidence value for 2001 and, subsequently, slightly underestimated λ_s .

Calculation of λ_s

The sibling risk ratio (λ_s) was calculated as:

$$\lambda_s = \frac{\text{No. of affected siblings of affected cases}}{\text{expected number of affected siblings (predicted by incidence data)}}$$

To minimize the effect of overestimating λ_s due to increased exposure to *N. meningitidis*, λ_s was recalculated using more than 1 week, 1, 3, 6, 9 and 12 months as cut-offs between the onset of MD in affected cases and their affected sibling(s). Given that all but two index cases had MD onset after 1990, at a time when chemoprophylactic treatment of family members and close contacts was widely practiced, stratification according to chemoprophylactic treatment administration was not carried out. In addition, for the two index cases with MD onset before 1991 (one in 1967 and the other in 1977), their affected siblings contracted MD 20 and 9.1 years respectively prior to the index case MD onset.

Role of socio-economic factors

To take into account the effect of socio-economic status, patients were classified according to the standard social class grading 1–5 provided by the Census Dissemination Unit, where geographical areas are broken down by socio-demographic characteristics, accessed by postcodes. In this grading, 1 and 5 indicate the most and least affluent areas respectively (http://census.ac.uk/cdu/Datasets/1991_Census_datasets/).

RESULTS

Over one thousand UK index cases were identified (621 MRF, 436 PICU, total 1057), of whom 648 (396 MRF and 252 PICU) completed a questionnaire (61.2% response rate). Excluded from the analysis were 15 pairs of monozygotic (MZ) twins and 34 non-Caucasian cases. Of UK Caucasian MD cases, 443 had at least one sibling and were included in the analysis.

There were 845 siblings of the 443 index cases. Of these, 27 were reported to have contracted MD. There were no significant differences in the proportions of affected sibs between the PICU and MRF groups (13 PICU, 14 MRF), nor in the mean (PICU 25.85 months, MRF 17.85 months) or median (PICU 0.5 months, MRF 1.5 months) intervals between dates of onset of infection in cases and their sibling(s). The two groups were therefore combined in all analyses.

Of the 27 affected sibling pairs, 11 (40.7%) contracted MD within 1 week of each other, 6 (22.2%) between 2 weeks and 1 month, 1 (3.7%) at 2 months, 1 (3.7%) at 8 months, 1 (3.7%) at 11 months and 7 (25.9%) after an interval of 12 months or more. Where over 12 months had elapsed between MD onsets, the range extended from 1.3–20 years. In all but one index case, all index cases had only one affected sibling. One index case had two affected siblings with both siblings contracting MD within 1 week of the index case.

The expected number of cases of MD in the 845 siblings estimated from age and calendar year specific population rates was 0.892. Compared with 27 observed cases of affected siblings, this gives a sibling risk ratio of 30.3 (95% CI 20–44).

In order to separate the relative effects of exposure to *N. meningitidis* from host factors (e.g. host genetic), values of λ_s were calculated using different exclusion

criteria (Table 1). The highest λ_s was for cases occurring within 1 week of each other. There was little difference in λ_s when there was more than 1 month between cases. Excluding pairs where the onset of the second case was more than 1 year after the date of onset of the index case, the sibling risk ratio was 8.2 (95% CI 3.3–17).

Index cases with affected siblings were distributed apparently randomly across all grades of socio-economic status with no obvious bias (grade 1, 22.7%; grade 2, 9.1%; grade 3, 18.2%; grade 4, 27.3%; grade 5, 22.7%) and no difference in social class distribution was found when MD cases were compared with the data for England and Wales ($P=0.5$). In addition, no difference in distribution of socio-economic status was found when the samples were stratified according to whether less than, or more than 1 month had elapsed between MD onset in index case and the affected sibling(s) ($P=0.9$).

DISCUSSION

This is the first study to quantify the increased risk of MD among siblings of affected cases. Siblings of affected cases are at a 30-fold increased risk of contracting MD. This increased risk of MD is due to both host (e.g. genetic) and environmental (e.g. exposure to *N. meningitidis*) factors. To minimize the risk of overestimating the contribution that host genetic factors make to the total λ_s value as a result of increased exposure to *N. meningitidis* in families with affected cases, the time elapsing between onset of MD in affected cases and their sibling(s) was taken into account. A cut-off point of 1 month was used as the effect of *N. meningitidis* co-exposure on the basis that acquisition would be minimal after this period given the practice of prophylactic treatment of all family members following initial disease, the relatively short time between acquisition and invasive MD [14–17], and the cumulative λ_s data presented in this study. Subject to this assumption, host genetic factors were found to contribute approximately one third ($\lambda_s=11$) of the overall increased risk of MD in siblings of primary cases ($\lambda_s=30$).

The response rate to the questionnaire was 61%, but as non-responders are unlikely to differ from responders in terms of genetic factors, the estimate of the sibling risk ratio should be unbiased by incomplete response. All index cases completing a questionnaire were asked about the number of full siblings, a variable unlikely to be affected by recall bias.

Another limitation of the study was the validity of the comparison of expected rates in siblings with those of the general population. It is possible that the siblings differed in terms of environmental risk factors for MD (such as smoking or low socio-economic status), which might have increased their risk of disease independently of a genetic effect [20]. This would tend to inflate the estimated sibling risk ratio, although as mentioned above, we tried to minimize such bias due to acute environmental exposure by excluding secondary cases occurring within one month of the index case. There was also no difference in the distribution of social classes between cases with MD and the general population of England and Wales, indicating that the sibling risk ratio was not likely to have been inflated due to an excess of affected sibling pairs of low socio-economic status.

It is possible that the λ_s value of 30 calculated in this study is an underestimation of the sibling risk. As the number of notifications recorded by the PHLS includes possible and probable as well as confirmed cases of MD, the age-specific incidence data might have been overestimated if some of the possible and probable cases were not in fact MD. If this was the case, the expected number of affected siblings predicted by the incidence data would have been lower and the overall λ_s value higher. In the calculation of λ_s , siblings of affected cases whose diagnosis was classified as possible or probable MD were excluded, thus avoiding λ_s overestimation. Notification of MD cases to the PHLS is known to be incomplete. However, given the severity of MD, it is more likely that cases are incorrectly reported as MD, rather than cases of MD not being reported at all.

Differences in bacterial virulence are undoubtedly important in determining the incidence of invasive disease as specific subgroups such as the ET-5 and ET-37 complex are implicated in global epidemics [21]. However, acquisition of a pathogenic strain is not sufficient to determine outcome, since even those colonized with the same subtype of organism do not develop MD. As early as 1945 Aycock and Mueller observed that, although MD incidence varied by season, meningococcal carriage did not, the implication being that carriage could not be the sole risk factor for MD [22]. Other studies have confirmed this and show no consistent relationship between the number of carriers in a community and the number of cases of disease [18, 23]. Episodes of upper respiratory tract infection may be a predisposing factor for occurrence of MD [24], however, the incidence of respiratory tract

infections is much higher than the incidence of MD and not all studies have found an association between those suffering from upper respiratory tract infections and invasive MD [25], indicating that other factors are important.

Given that acquisition and carriage of *N. meningitidis* are not sufficient for disease, the host genetic contribution to the increased risk of MD in siblings is probably more than one third of the total risk, as there is likely to be a genetic component to susceptibility even within siblings who contract MD within one month of the index case.

Why *N. meningitidis* shows a dichotomy between a 'silent' process (carriage in the upper respiratory tract) and an overt disease process (invasive disease) is unknown. This study has highlighted a greatly increased risk of MD amongst siblings of affected cases and has provided an estimate that host genetics may contribute approximately one third of this total risk. In view of the incomplete protection offered to siblings of cases of MD by administration of prophylactic antibiotics, the demonstration of a substantial host genetic component of risk of MD amongst siblings of cases reinforces the need for very careful counselling of family members of index cases, and the need to ensure a high level of familiarity within this group of the signs and symptoms of MD.

Accurately calculating λ_s for an infectious disease is difficult given the increased risk of exposure to infection in family members compared with the general population and the variation in disease risk according to age and calendar year. To our knowledge this is the first time that λ_s has been calculated for an infectious disease where both these factors have been taken into account. The methods used here may give a clearer indication of the overall role of host genetics in other infectious diseases.

ACKNOWLEDGMENTS

We would like to thank the PHLS and ONS for supplying data on meningococcal notifications and population levels respectively, Dr Norman Cobley from the Epidemiology and Public Health Department at St Mary's Hospital for supplying data on socio-economic distributions, the Meningococcal Research Group (Dr Simon Nadel, Ms Rachel Galassini, and Professor Simon Kroll) which helped organize the questionnaires, and the Meningitis Research Foundation and MRC for funding.

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