Heritability of Recurrent Tonsillitis

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Objective: To estimate the relative contribution of genetic and environmental effects on the variance in the liability of recurrent tonsillitis.

Design: Retrospective questionnaire data from a population-based cohort.


Participants: A total of 9479 Norwegian twins born between January 1, 1967, and December 31, 1979, identified through the Medical Birth Registry of Norway.

Main Outcome Measure: Recurrent tonsillitis.

Results: The lifetime prevalence of recurrent tonsillitis was 11.7% (95% confidence interval, 11.0%-12.3%), with a significant predominance of female cases. The tetrachoric correlations for monozygotic twins were 0.71 for males and 0.60 for females. For dizygotic twins, the correlations were 0.12 for males, 0.14 for females, and 0.24 for dizygotic pairs of opposite sex. Structural equation modeling indicated that genetic effects explained 62% of the variation in the liability of recurrent tonsillitis. The remaining variance was attributed to individual environmental effects. There was no evidence of sex-specific genetic effects on the liability of recurrent tonsillitis.

Conclusion: There is evidence for a substantial genetic predisposition for recurrent tonsillitis.


Tonsillitis is a common childhood infectious disease that involves the parenchyma of the palatine tonsils. Although tonsillitis has few long-term effects, recurrent tonsillitis causes significant morbidity and time lost from school or work.1 The definition of recurrent may vary somewhat, but the criteria used recently as a measure of severity were 5 or more episodes of true tonsillitis per year, symptoms recurring for at least a year, and episodes that are disabling and that prevent normal functioning.1 In children, sore throat may be part of the early symptom complex of upper respiratory tract morbidity. Although most other childhood upper respiratory tract diseases tend to improve with time, there is no evidence of spontaneous resolution of recurrent tonsillitis.2 The limited data available provide no evidence of a difference between surgical and medical treatment for recurrent tonsillitis.1 To date, neither genetic nor environmental risk factors for tonsillitis have been fully explored. A previous case-control study1 reported that parental atopy and parental history of tonsillectomy predict subsequent tonsillitis in their children. Familial clustering of tonsillectomy has been shown in a small clinical study,4 but the study was not designed to distinguish between these 2 sources of variance. Another study5 reported that heritability of tonsillectomy varies with time, suggesting a cohort effect in the heritability of this phenotype. To our knowledge, the heritability of recurrent tonsillitis has not previously been reported. The aim of the present study is to estimate the relative contribution of genetic and environmental effects in the liability of recurrent tonsillitis in a population-based data sample of Norwegian twins.

Methods

Sample

The Norwegian Institute of Public Health Twin Study has a dynamic cohort design. The current database includes information on twins born between January 1, 1967, and December 31, 1979, identified through the Medical Birth Registry of Norway. Two questionnaire studies have been conducted so far, in 1992 and 1998, with individual response rates of 73% and 63% and pairwise response rates of 64% and 52%, respectively. The 1992 questionn...
naire was sent to all Norwegian twins born between January 1, 1967, and December 31, 1974, who were at least 18 years old and from whom a current address in Norway was obtained. The 1998 questionnaire was sent to all twins who had received the 1992 questionnaire plus 5 new birth cohorts including twins born between January 1, 1975, and December 31, 1979. The combined 1992 and 1998 questionnaire sample includes 9479 twins who completed at least 1 of the questionnaires; 4430 twins participated in both studies. The number of pairs responding to each of the questionnaires and the number of pairs included in the combined sample, by sex and zygosity, are given in Table 1. The twin research program, including procedures and zygosity determination, is described in detail elsewhere.6,7

Both questionnaires included the following item about tonsillitis: “Do you have or have you had recurrent tonsillitis?” For this study, we assumed that individuals who reported recurrent tonsillitis at least once have had the disease. Accordingly, all the individuals who reported recurrent tonsillitis on at least 1 of the questionnaires were included as cases.

### Table 1. Questionnaire Responders by Sex and Zygosity

<table>
<thead>
<tr>
<th>Group</th>
<th>1992 Questionnaire</th>
<th>1998 Questionnaire</th>
<th>Combined Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZM</td>
<td>416</td>
<td>528</td>
<td>677</td>
</tr>
<tr>
<td>MZF</td>
<td>528</td>
<td>777</td>
<td>904</td>
</tr>
<tr>
<td>DZM</td>
<td>387</td>
<td>397</td>
<td>592</td>
</tr>
<tr>
<td>DZF</td>
<td>443</td>
<td>655</td>
<td>789</td>
</tr>
<tr>
<td>DZU</td>
<td>796</td>
<td>979</td>
<td>1285</td>
</tr>
<tr>
<td>Total</td>
<td>2570</td>
<td>3334</td>
<td>4247</td>
</tr>
</tbody>
</table>

Abbreviations: DZF, dizygotic females; DZM, dizygotic males; DZU, dizygotic unlike sex; MZF, monozygotic females; MZM, monozygotic males.

**ANALYSIS**

Structural equation modeling was used to estimate the relative contribution of genes and environment in the liability of recurrent tonsillitis. The method is frequently used in twin data analysis and is described in detail elsewhere.8

Co-twin similarity was calculated as tetrachoric correlations for 5 groups defined by sex and zygosity (ie, monozygotic male, monozygotic female, dizygotic male, dizygotic female, and dizygotic opposite-sex pairs) using a computer program (Mx; M. C. Neale, Richmond, Va).9 A tetrachoric correlation can be defined as a correlation coefficient computed for 2 normally distributed measures that have been expressed as a dichotomy. In our application, the calculation of tetrachoric correlation is based on the assumption of an underlying normally distributed liability of recurrent tonsillitis in which manifest disease occurs when a certain threshold is reached. There is no simple formula to derive a tetrachoric correlation; it must be estimated iteratively using a computer program. The expected value of the tetrachoric correlation between 2 dichotomous variables is identical to the Pearson correlation between the 2 corresponding normally distributed disease liabilities. A path model that specifies how genetic and environmental factors contribute to twin resemblance is depicted in the Figure. When using these models, the variation in the liability of recurrent tonsillitis is decomposed into effects of unobserved latent factors. The observed phenotype, recurrent tonsillitis, for twin 1 and twin 2 in a pair is specified as $P_1$ and $P_2$, respectively. Genetic factors comprise additive ($a$) and dominant ($d$) effects. Additive genetic effects refer to the summed effects of the individual alleles at all loci. Dominant effects are intralocus interactions in which a single allele at a particular locus has more than half the effect on phenotypic expression than the pair of alleles. Parameterization of the model is based on biometric expectations whereby identical twins share all their genes and fraternal twins share, on average, half of their segregating genes. Thus, identical twins are perfectly correlated for effects owing to genetic dominance and additive genetic effects, and fraternal twins are correlated 0.5 for additive genetic effects and 0.25 for genetic dominance. Environmental factors are partitioned into common ($c$) and specific ($e$) environment. Common environment refers to environmental factors shared by the twins and are therefore perfectly correlated in both zygosity groups. Specific environmental factors contain nonshared environmental factors and measurement error. Specific environmental factors contribute to differences within a pair.

In the analysis, structural equation models that specify the expected variance-covariance structure are fitted to the observed twin data. Estimates of the genetic and environmental contribution to the variance in disease liability are represented by their respective path coefficients, $a$, $d$, $c$, and $e$, connecting the latent factors to the phenotype as shown in the Figure. These path coefficients are standardized partial regression coefficients. The proportion of the total phenotypic variance attributable to each factor is obtained by squaring the value of the standardized path coefficient. The broad-sense heritability of recurrent tonsillitis can be estimated as $h^2 = a^2 + d^2$, and the total variance due to environmental factors is $c^2 + e^2$. By definition, $a^2 + d^2 + c^2 + e^2 = 1$.

Models were fitted by means of maximum likelihood estimation using a computer program (Mx).9 The equality of the liability thresholds within twin pairs and across sex and zygosity was tested to check for prevalence differences among groups. A series of hierarchal models were fitted to the raw data, and ACE and ADE models are compared with nested submodels, in which additional parameters are fixed to zero in a stepwise manner. The parameter is significant when a model that excludes this parameter yields a significantly worse fit than the model that includes this parameter. A model with only genetic dominance and no genetic additive effect is not realistic because even under full dominance, most of the genetic variance will usually be additive10; therefore, $d$ was constrained not to exceed $a$ in the models tested.

The models were also expanded to test for sex differences. General sex limitation models allow the genetic source and the
genetic magnitude of variance to differ between males and females. Common sex limitation models are more restricted in that identical sets of genes contribute to the phenotypic variation, but the magnitude of genetic and environmental effects is allowed to vary across sexes. Models of no sex limitation restrict the genetic source and the genetic magnitude of variance to be equal in males and females. The goodness-of-fit for the different models was evaluated according to the Akaike Information Criterion ($\Delta \chi^2 - 2df$), in which the model with the lowest Akaike Information Criterion value fits the observed data best. Twin studies provide a method for detecting selection bias. There are no available data on the nonresponders, which would provide a test of the representativity of the sample. However, co-twins are correlated for most phenotypes, and a selection bias would be expected to cause statistical deviations among the nonresponders’ co-twins as well. This deviation among single responders should be weaker than among nonresponders but in the same direction. To check for such an indicator of selection bias, we compared the liability threshold for recurrent tonsillitis in pair responders and single responders.

### RESULTS

#### PREVALENCE AND CORRELATIONS

The prevalence of recurrent tonsillitis was 11.7% (95% confidence interval, 11.0%-12.3%), and it differed significantly between females (14.1%; 95% confidence interval, 13.1%-15.0%) and males (8.8%; 95% confidence interval, 7.9%-9.6%). The tetrachoric correlations between recurrent tonsillitis in twin 1 and twin 2 in a pair are greater among monozygotic twins (males, 0.71; females, 0.60) than among dizygotic twins (males, 0.12; females, 0.14; opposite sex, 0.24), indicating genetic variance.

#### MODEL FITTING

Sex differences in the liability threshold values were statistically significant, but there were no differences in the thresholds among zygosity groups within the same sex. Thresholds did not differ statistically significantly for complete and incomplete pairs. In accordance with this homogeneity of thresholds, subsequent model fitting specified different thresholds in males and females and equal thresholds in monozygotic and dizygotic twins within the same sex. The dizygotic twin correlation was less than half the correlation in the monozygotic twins, suggesting that genetic dominance is important. Therefore, the ADE general sex limitation model was chosen as the full model. The effect of genetic dominance was constrained not to exceed the size of the additive genetic effect in all the models tested. Table 2 provides results from the model-fitting procedures. The models start with the least-constrained model, subsequently adding constraints and comparing more parsimonious models with the full model. In model 1, the genetic correlation was estimated to be close to 1, and this parameter could be fixed to 1 in the following models without any loss in fit. The significance of the $d$-parameter is reflected in the Akaike Information Criterion difference between models 3 and 4 ($-2.0$ vs $94.7$) and between models 5 and 6 ($-6.4$ vs $151.5$), indicating that the ADE model was a better fit than the AE model in the common sex limitation model and in the model without sex limitation. According to the Akaike Information Criterion, the no sex limitation ADE model yielded the best fit. In this model, additive genetic effects explain 31% (95% confidence interval, 27%-35%) of the variance, and genetic dominance accounts for 31% (95% confidence interval, 27%-35%) of the variance. The remaining 38% (95% confidence interval, 30%-46%) of the variance is explained by individual environmental effects.

#### COMMENT

To our knowledge, the present study is the first to explore the heritability of tonsillitis. The study revealed a considerable genetic predisposition for tonsillitis with additive and genetic dominance effects. No sex differences were found in the genetic source or the size of the heritability estimates.

### PREVALENCE

We found that the prevalence of self-reported recurrent tonsillitis was 11.7% (95% confidence interval, 11.0%-12.3%), with a significant predominance of female cases. Except for a prevalence estimate of 12.1% for recurrent tonsillitis in primary schoolchildren in Turkey, there are, to our knowledge, no comparable epidemiologic prevalence studies because most reports are limited to specific bacterial agents or the effects of antibiotic drug treatment. In the evaluation of the clinical evidence for...
the effectiveness of tonsillectomy vs medical treatment, 5 or more episodes were required for the diagnosis of recurrent tonsillitis. In contrast to the clinical definition of tonsillitis of Paradise et al from 1984, our disease classification was not based on an operational definition from symptoms, disease severity, or number of episodes but on a simple question about ever having experienced recurrent tonsillitis. The prevalence estimate in our study may be affected by different interpretations of the term recurrent tonsillitis, and a confounding of tonsillitis and pharyngitis cannot be ruled out.

Despite the widespread use of self-reported data in epidemiologic research, there is a marked paucity of studies that address the validity of such data. Evaluation of the validity of self-reported tonsillitis has, to our knowledge, not previously been reported. Although we do not have direct validation of the term recurrent tonsillitis in our questionnaire, studies investigating the validity of other health measures find that self-reports in general reflect medical conditions. Moderate-to-good agreement between self-report and medical records has been found for tonsillectomy and adenoidectomy in 2 studies. Good agreement was demonstrated for recurrent otitis media comparing self-report and medical records, especially for severe cases that required a visit to an ear, nose, and throat specialist or middle ear surgery. Moderate agreement between self-report and medical records was reported for ever having had asthma. In a review article of agreement between self-report questionnaire data and medical records, hay fever, asthma, sinusitis, and chronic bronchitis were all more likely to be reported by the respondent than in the medical record, indicating disease overreporting. Fairly accurate recall of previous hospitalization and surgery was found in the same study. Based on these finding, there might be overreporting of recurrent tonsillitis in our data.

Comparing 2 different methods of self-report, participants tended to forget less severe medical conditions when questionnaire data were compared with in-person interviews. Underreporting of recurrent tonsillitis cannot be ruled out in our study if the disease was regarded as a nonsignificant health problem, and only the severe cases that require medical or surgical treatment may have reported tonsillitis in our questionnaire. Recall bias may occur in retrospective reports of childhood disease. This may, in turn, inflate or deflate the prevalence estimate.

GENETIC AND ENVIRONMENTAL EFFECTS

As far as we know, the present study is the first to explore the heritability of tonsillitis. In earlier studies, familial clustering of tonsillectomy has been reported, but the studies did not resolve whether the sources of variance were of genetic or environmental origin. The environmental effect may, to some extent, be affected by external factors, such as differences in attitude and criteria for surgery, parental preferences for their child, and national priorities in health care. Martin et al reported that genetic factors were important in predisposition to tonsillectomy. Genetic factors, both additive genetic factors and genetic dominance, explained 62% of the variance in recurrent tonsillitis. Our use of self-reported data may, to some extent, have biased the heritability estimates. Heritability may be somewhat underestimated if nonshared environment is inflated by random sources of error that are not correlated within the twin pair. A positive history of tonsillitis in one twin may increase the awareness of symptoms of tonsillitis in the co-twin, and such reporting bias may be higher for monozygotic pairs than for dizygotic pairs. Because we did not find any prevalence differences in recurrent tonsillitis between monozygotic and dizygotic twins within the same sex, this potential reporting bias does not seem relevant to our data. Furthermore, we found no evidence that refusal to participate in our study was systematically related to tonsillitis reports.

Quantitative genetic studies are a preliminary step to identify heritable phenotypes that should be further examined at the molecular-genetic level. Our study found evidence of a substantial genetic effect that may be related to anatomy, immunologic defense mechanisms, or both. It is well known that the Waldeyer tonsillar ring exerts regional immune functions when exposed to airborne and alimentary antigens. Morphologic studies have found significant changes in the local innate and acquired bacterial defense systems during acute tonsillitis, such as increased lysozyme and lactoferrin coating of the bacteria and reduced secretory IgA levels. Furthermore, increased carrier rates of pathogenic bacteria are found in children after tonsillectomy. The increase in specific cytokines during tonsillitis suggests a continuous up-regulation of immunocompetent cells. It has been reported that tonsillitis speeds up the age-related involution of the tonsils as immunologic organs. A subsequent recommendation has been to show a conservative attitude to adenotonsillectomy, especially in young age groups.

Schilder et al reported a significant correlation between acute tonsillitis and acute otitis media in the same child. The same study claimed that the common cold is the ubiquitous upper airway disease and that accompanying morbidity, such as tonsillitis and otitis media, depends on the predisposition of the child. Such predisposition could be genetic or environmental in origin. For otitis media, a substantial additive genetic predisposition has been reported. In contrast to genetic effects reported for otitis media, the heritability of tonsillitis was composed of additive and genetic dominance effects. This suggests a difference in at least part of the predisposition for otitis media and tonsillitis.

The identification of children who are at risk for upper respiratory tract morbidity adds valuable information to help identify individuals in need of preventive and prophylactic strategies. The present study provides evidence of a substantial genetic predisposition for tonsillitis, suggesting that genetic dominance and additive genetic effects contribute to the disease predisposition.

Submitted for Publication: January 25, 2005; accepted February 2, 2005.

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Funding/Support: The Norwegian Institute of Public Health program of twin research is supported by grants from the Norwegian Research Council and the Norwegian Foundation for Health and Rehabilitation (Oslo), and the European Commission (Brussels, Belgium) under the program “Quality of Life and Management of the Living Resources” of the Fifth Framework Programme (QLG2-CT-2002-01254).

Acknowledgment: We thank the twins for their participation.

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