Club foot
A TWIN STUDY

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The aetiology of congenital club foot is unclear. Although studies on populations, families and twins suggest a genetic component, the mode of inheritance does not comply with distinctive patterns.

The Odense-based Danish Twin Registry contains data on all 73000 twin pairs born in Denmark over the last 130 years. In 2002 all 46418 twins born between 1931 and 1982 received a 17-page questionnaire, one question of which was ‘Were you born with club foot?’ A total of 94 twins answered ‘Yes’, giving an overall self-reported prevalence of congenital club foot of 0.0027 (95% confidence interval (CI) 0.0022 to 0.0034). We identified 55 complete twin pairs, representing 12 monozygotic, 22 dizygotic same sex (DZss), 18 dizygotic opposite sex (DZos) and three unclassified. Two monozygotic and 2 DZss pairs were discordant. The pairwise concordance was 0.17 (95% CI 0.02 to 0.48) for monozygotic, 0.09 (95% CI 0.01 to 0.32) for DZos and 0.05 (95% CI 0.006 to 0.18) for all dizygotic (DZos) twins.

We have found evidence of a genetic component in congenital club foot, although non-genetic factors must play a predominant role.

The aetiology of congenital club foot is speculative and the influence of genetic factors is unclear. Although studies on populations, families and twins suggest a genetic component, the mode of inheritance does not fit classical patterns. Conversely, all segregation analyses on populations with clubfoot suggest a single, major genetic factor. Twin studies are useful in determining whether or not the cause of a disorder is genetic. Monozygotic twins have identical genes, dizygotic twins share 50% of their genes, and all twins share the same environment antenatally. With regard to congenital disorders it is therefore possible to study the effect of genetic factors. Increased rates of doubly affected monozygotic twins compared with dizygotic twins (concordance) indicate a genetic aetiology to a disorder. In 1939 the first twin study on club foot was published by Idelberger. In 174 pairs, the pairwise concordance was 0.33 for monozygotic and 0.03 for dizygotic with the same sex (DZos). Based on these findings, if one monozygotic twin is born with club foot the risk of the second having the condition was reported to be 1 in 3, indicating a partly genetic aetiology. Idelberger’s study population of 242 patients was obtained by combining a disease register on 11459 patients with club foot with regional registers on twin births. This method is disease-based and therefore theoretically inferior to a population-based study.

The purpose of our study was to establish a congenital club foot twin cohort that would enable more accurate estimation of concordance than was hitherto possible.

Patients and Methods
The Odense-based Danish Twin Registry is unique as it contains data on all 73000 pairs of twins born in Denmark over the last 130 years. It was the first population-based twin registry and one of the largest cohorts in the world.

In spring 2002 all twins registered in the Danish Twin Registry born between 1931 and 1982 were sent a 17-page questionnaire. The establishment of zygosity in the Danish Twin Registry is 95% accurate and based on a validated method consisting of four questions of similarity. All scientific ethical committees in Denmark approved the study.

Concordance, as opposed to discordance, is when both of a twin pair are affected. Pairwise concordance is the proportion of discordant pairs compared with the total number of affected pairs. It estimates the probability of both twins in a pair being affected when one is. If there are more discordant monozygotic than dizygotic pairs this is evidence of a genetic component to the disease.
Table I. Overview of the 55 complete twin pairs (three were unclassified)

<table>
<thead>
<tr>
<th></th>
<th>Monozygotic</th>
<th>Dizygotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pairs</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Both twins affected</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>One twin affected</td>
<td>22</td>
<td>38</td>
</tr>
</tbody>
</table>

The affected twin is known as the proband. The probandwise concordance is the proportion of affected twins to probands compared with the total number of probands. It estimates the probability that one twin in a pair is affected where the other twin is, and can be compared with the risk of other relatives and the population in general.9

In a Mendelian inheritance the probandwise concordance for monozygotic twins is 1 (all affected) and for dizygotic twins is 0.5 for dominant (50% affected) and 0.25 for recessive traits. Concordance less than 1 in monozygotic twins is evidence of factors other than genetic.

Statistical methods. The prevalence of self-reported congenital club foot was calculated and stratified according to gender. The pairwise and probandwise concordances were calculated and compared with the chi-squared test using the statistical software package SPSS, version 6.1 (SPSS Inc., Chicago, Illinois). As all cases are probands, we used the casewise concordance as the maximum likelihood estimate and calculated the 95% confidence interval (CI) according to the standard error of this, as described by Hopper.10

Results

The questionnaires were sent to 46 418 twins and returned by 34 944 (75%). Of the responders, 34 485 (15 731 males and 18 754 females) answered the question ‘Were you born with club foot?’, 94 said ‘Yes’, giving an overall self-reported prevalence of congenital club foot of 0.0027 (95% CI 0.0022 to 0.0034), with male and female prevalence of 0.0031 (95% CI 0.0022 to 0.0041) and 0.0025 (95% CI 0.0022 to 0.0034), respectively (p = 0.29).
The question was answered by 55 twin pairs, representing 12 monozygotic, 22 DZss, 18 dizygotic other sex (DZos) and three unclassified. There were four pairs who were concordant, two monozygotic and two DZss (Table I). The pairwise concordance was 0.17 (95% CI 0.02 to 0.48) for monozygotic, 0.09 (95% CI 0.01 to 0.32) for DZss and 0.05 (95% CI 0.006 to 0.18) for all dizygotic (DZtot). The probandwise concordance was 0.29 (95% CI 0.07 to 0.51) for monozygotic, 0.17 (95% CI 0.05 to 0.29) for DZss and 0.10 (95% CI 0.04 to 0.16) for DZtot.

Discussion

Twin studies are unique discriminators of the contribution of genetic and environmental factors to the phenotype. This discrimination is purest in a congenital disease, as any influences from the postnatal environment are avoided. It is essential that any twin cohort be population-based, as disease-based studies tend to over-represent monozygotic and concordant pairs.9

The Danish Twin Registry is population-based and of high validity. However, because zygosity was determined by questionnaire, a practicable method in studies of this size, this might affect the identification of zygosity. The frequency of misclassification was no higher than 5%.8

The major challenge of questionnaire-based studies is to identify the patients. In this study on congenital club foot we consider the method to be reliable, as the disorder is not easily overlooked or mistaken for another. We do not expect patients to be unaware of having congenital club foot, however well corrected. We therefore regard the self-reported prevalence of 0.0027 in this large cohort as reliable. In a Scandinavian population, the incidence was previously reported to be 1 in 1000 live births.11 There is no evidence of an increased risk of club foot in twins.1 In a congenital benign chronic disease the prevalence is identical to the incidence. As club foot is sometimes syndromic one would expect the prevalence to be slightly lower than the incidence, owing to a higher mortality in these few patients. It is surprising that we did not find a difference between the sexes, as a male to female ratio of 2:1 is generally reported.1,11-15

According to Idelberger,6 both twins are affected in a third of monozygotic pairs and 1 in 35 of DZss pairs. We found that both twins were affected in a sixth of monozygotic pairs, 1 in 11 of DZss pairs, and 1 in 20 of DZtot pairs. The probandwise concordance of 0.29 confirms that the risk of a second monozygotic twin having a club foot is 1 in 3. However, in spite of the size of the cohort these figures have wide confidence intervals.

Although non-genetic factors must play a significant role in this study or publication.

References


