

Genetic associations between frozen shoulder and tennis elbow: a female twin study

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Objectives. To estimate the heritability of frozen shoulder (FS) and tennis elbow (TE) and to examine the two disorders for possible genetic or environmental associations.

Methods. Self-reporting questionnaire data on risk factors for, and a physician diagnosis of, FS or TE were obtained from 865 monozygotic (MZ) and 963 dizygotic (DZ) unselected female twin pairs aged between 20 and 76 yr registered with the St Thomas' UK Adult Twin Registry. The heritability of each disorder was estimated in a classic twin study. The association between FS and TE was then explored by log-linear modelling comparing MZ with DZ individuals and twin pairs for the presence of both disorders.

Results. The prevalence of FS and TE were 11.6 and 16.7%, respectively. A heritability of 42% was estimated for FS and 40% for TE after adjusting for age. There was no confounding by environmental risk factors. Log-linear modelling demonstrated FS and TE, independently, to be associated within members of a twin pair and confirmed a stronger association in MZ than DZ pairs. In addition the two disorders occurred together 2–3 times more frequently in individuals than would be expected by chance. However, there was no association between FS and TE across members of a twin pair, implying no evidence for a shared genetic component to the two disorders.

Conclusions. Genetic factors are implicated in the aetiology of both frozen shoulder and tennis elbow but are independent of each other. The two disorders occur together 2–3 times more frequently than by chance in individuals. However, the association is most likely mediated by individual-specific environmental factors common to the two conditions and not by a common genetic susceptibility.

KEY WORDS: Frozen shoulder, Tennis elbow, Tendonitis, Twins, Genetic epidemiology.

Studies of the epidemiology of frozen shoulder and tennis elbow have mainly focused on exposure to environmental and occupational risk factors [1, 2] and have not considered the genetic basis for these disorders. The contribution of genetic factors to the aetiology of a wide spectrum of rheumatic conditions is increasingly recognized as important. Recent evidence suggests that soft tissue conditions also have a genetic basis [3]. In this study we use the classic twin model involving monozygotic (MZ) and dizygotic (DZ) twins to assess the relative genetic and environmental contribution to frozen shoulder and tennis elbow. We also look at individuals for evidence of an association between both disorders

that might suggest a common underlying susceptibility to disease, and explore whether this could be accounted for by shared genetic factors.

Methods

The subjects comprised volunteer female–female twin pairs recruited from the St Thomas' UK Adult Registry. The characteristics of the twins have been shown to be similar to those of a general population [4], their zygosity previously determined by a standard questionnaire and no participant was aware of any specific hypothesis related to the study of soft tissue disorders.

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Submitted 10 June 2002; revised version accepted 9 October 2002.

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Self-reporting questionnaires were returned by 1828 twin pairs (865 MZ and 963 DZ) and 832 singletons (overall response rate 68%) and data collected on relevant risk factors [1, 2] including age, height, weight, physical activity, occupation, parity, menopausal status and a physician diagnosis of diabetes mellitus, frozen shoulder and tennis elbow.

To examine disease recall a random sample of 125 MZ and 125 DZ twin pairs, in whom one or both twin had reported FS or TE, was sent a second questionnaire after 12 months. Individuals were also asked if their symptoms persisted or had resolved. The general practice notes for a random sample of 250 MZ and 250 DZ individuals with either FS or TE were also reviewed. Cases with documented evidence of a diagnosis were compared with those without for differences in characteristics and exposure to environmental risk factors.

Analysis

We used a three-stage approach in the analysis: (i) estimating the heritability of each disorder, (ii) assessing the degree of association between the two disorders in individuals and (iii) examining this association for evidence of a common genetic liability.

The presence of a genetic influence was assessed through case-wise concordance (P_c), which is a measure of the probability of a co-twin being affected if their twin has the disorder. A greater concordance in MZ than DZ twin pairs, in the presence of similar levels of exposure to environmental factors, indicates the likely presence of a genetic component.

Concordance in itself is not a direct reflection of the underlying size of genetic liability as it is affected by the prevalence of a disease or phenotype. Genetic liability is more appropriately assessed through heritability. For discontinuous traits, this requires the assumption that the trait is determined by a continuous underlying liability. Heritability is then a measure of the extent to which genetic variation accounts for the variance in the underlying liability to the trait in the population. Heritability was estimated using an implementation of DeFries–Fulker regression [5].

Log-linear modelling was used to assess the association between frozen shoulder and tennis elbow in individuals and the genetic and environmental contribution to this. The statistical approach considers the full distribution of the concordance data for MZ and DZ twins for frozen shoulder and tennis elbow both independently and together [6]. Models were constructed to best explain this $2 \times 2 \times 2 \times 2$ distribution in terms of a set of parameters representing: (i) the prevalence of disease, (ii) the association within individuals and (iii) the association within twin pairs.

Binary variables F_1 and F_2 were used to define frozen shoulder in each member of the twin pair; similarly T_1 and T_2 for tennis elbow (Table 2). Under symmetry, the prevalence of cases in the sample as a whole was defined by two variables, $F = F_1 + F_2$ and $T = T_1 + T_2$. Interaction terms were defined to explain the distribution of frozen shoulder in both twins ($FF = F_1 \times F_2$) and tennis elbow ($TT = T_1 \times T_2$), and the occurrence of both disorders in the same individual [$FT = (F_1 \times T_1) + (F_2 \times T_2)$]. The association between frozen shoulder and tennis elbow across members of a twin pair was explained by two terms: (i) $FXT = (F_1 \times T_2) + (F_2 \times T_1)$, representing the occurrence of frozen shoulder in one twin and tennis elbow in the other and vice versa; and (ii) $FFTT = FF \times TT$, the occurrence of both disorders in both twins.

The model that best described the distribution of the two disorders in the data was developed by the sequential addition of interaction terms and comparing the likelihood ratio based on 'goodness of fit'. The parameters of the best fitting model were converted to odds ratios by exponentiation.

Results

The prevalence of frozen shoulder was 10.4% in MZ and 12.7% in DZ twins. The respective values for tennis elbow were 17.8% and 15.8%.

Age, height, weight, body mass index, activity levels, occupation, parity, menopausal status and presence of diabetes mellitus showed no significant differences between the zygosity groups or between singleton and paired responders. The prevalence of both disorders increased with age but no environmental risk factor was found to have a significant effect on either frozen shoulder or tennis elbow in our population.

With regard to disease recall and diagnosis, an 85% response was achieved for the second questionnaire and the correlation between first and second questionnaire for the diagnosis of FS or TE was high with a Kappa value 0.94 regardless of whether disease persisted or had resolved. General practice records were available for 385 (77%) cases and of these, 181 cases (47%) had documented evidence of either disorder. No differences in characteristics or exposure to environmental risk factors were found between those with or without documented disease.

The number of concordant and discordant pairs, the case-wise concordance and the heritability estimates for frozen shoulder and tennis elbow are shown in Table 1.

TABLE 1. The distribution of concordant and discordant twin pairs, case-wise concordance and heritability estimates for frozen shoulder and tennis elbow (95% confidence intervals)

Variable	Frozen shoulder		Tennis elbow	
	MZ	DZ	MZ	DZ
Number of concordant pairs	27	30	59	40
Number of discordant pairs	126	184	191	224
Case-wise concordance ^a	0.30 (0.21–0.39)	0.25 (0.17–0.32)	0.38 (0.31–0.45)	0.26 (0.20–0.33)
Crude heritability	0.49 (0.36–0.62)		0.45 (0.34–0.57)	
Age-adjusted heritability	0.42 (0.28–0.55)		0.40 (0.29–0.52)	

^aCase-wise concordance calculated using the formula: $2Nc/(2Nc + Nd)$, where Nc is the number of concordant pairs and Nd the number of discordant pairs.

Case-wise concordance in MZ pairs exceeded that in DZ pairs in both frozen shoulder and tennis elbow implying a genetic component to each disorder. These differences translated into a heritability of 42% for frozen shoulder and 40% for tennis elbow, with a small effect of age and no confounding effect from environmental factors.

The distribution of frozen shoulder and tennis elbow among twin pairs by zygosity is shown in Table 2. In the log-linear analysis, the model that best explained the data in the MZ and DZ groups separately required the parameters *F*, *T*, *FF*, *TT* and *FT* only. Odds ratios (OR) for the presence of frozen shoulder or tennis elbow in both twins were consistent with the heritability estimates, showing higher values for MZ than DZ twin pairs (Table 3). The best fitting model showed an association between frozen shoulder and tennis elbow in an individual [OR of 3.40 (CI 2.35–4.93) for MZs and 2.37 (CI 1.71–3.27) for DZs] but no association across twin pairs. Higher order terms such as *FXT* and *FFTT* were not required to explain the distribution of the data. Thus there was no evidence for either shared genetic or environmental factors as the presence of one disorder in a twin did not increase the risk of the other disorder in their co-twin.

TABLE 2. The number of twin pairs by zygosity, frozen shoulder and tennis elbow status

Frozen shoulder		Tennis elbow		Number of twin pairs			
Twin 1	Twin 2	Twin 1	Twin 2	MZ (<i>n</i> =865)		DZ (<i>n</i> =963)	
F1	F2	T1	T2	No.	%	No.	%
0	0	0	0	537	62.0	573	59.5
0	0	0	1	68	7.8	75	7.8
0	0	1	0	66	7.6	74	7.7
0	0	1	1	42	4.8	27	2.8
0	1	0	0	36	4.2	55	5.7
0	1	0	1	16	1.8	21	2.2
0	1	1	0	6	0.7	11	1.1
0	1	1	1	5	0.6	5	0.5
1	0	0	0	31	3.6	55	5.7
1	0	0	1	5	0.6	11	1.1
1	0	1	0	20	2.3	21	2.2
1	0	1	1	7	0.8	5	0.5
1	1	0	0	12	1.4	16	1.7
1	1	0	1	5	0.6	5	0.5
1	1	1	0	5	0.6	5	0.5
1	1	1	1	5	0.6	4	0.4

TABLE 3. Odds ratios (95% confidence intervals) estimated from log-linear modelling

Association	MZ pairs	DZ pairs
Frozen shoulder in both twins	4.96 (2.86–8.62)	2.53 (1.56–4.08)
Tennis elbow in both twins	4.07 (2.71–6.11)	2.21 (1.45–3.37)
Frozen shoulder and tennis elbow in the same twin	3.40 (2.35–4.93)	2.37 (1.71–3.27)
Frozen shoulder in one twin and tennis elbow in the other	0.79 (0.52–1.22)	1.11 (0.77–1.60)
Test of fit (χ^2_9)	4.90	3.35
Probability	0.84	0.95

Discussion

This study is the first to report a genetic component to both frozen shoulder and tennis elbow. To our knowledge it is also the first to identify a 2–3-fold increased risk for both disorders occurring in the same individual. The genetic components are independent for each disorder as there is no evidence for aggregation within twin pairs. The increased risk of having both disorders is therefore most likely to be mediated by individual-specific environmental factors.

Epidemiological studies of soft tissue injury have focused principally on environmental risk. We have now demonstrated that genetic factors also play an important role in the pathogenesis of these disorders. Research into the mechanisms by which genes influence soft tissue disorders and interact with the environment is required. These mechanisms remain open to speculation but abnormalities of collagen metabolism and nerve physiology might offer some insight. For example, several cytokine and cellular processes of collagen degradation and tendon repair have been identified [7]. By appreciating the nature of gene defects and their effect on collagen and fibrin structure, we also have a better understanding of the pathogenesis of the more common heritable connective tissue diseases [8]. Susceptibility to injury could also arise from gross anatomical variations such as shortened tendon length or increased tendon laxity. As yet unidentified genetically determined and subtle abnormalities of collagen metabolism, tendon repair or structure might occur in the general population and increase the risk of soft tissue injury.

Altered nerve function could constitute another mechanism leading to soft tissue injury. Nerve damage and new patterns of pain behaviour have been observed in animal models and studies in mice suggest that mechanical, chemical and thermal nociception display moderate to high levels of heritability [9, 10]. In human studies, cases with repetitive injury and non-specific arm pain have been shown to have an altered function of the median nerve [11]. It is not clear which comes first, an abnormality of the nerve leading to injury or vice versa, but it is possible that abnormalities around or within nerves could bring about an alteration in joint proprioception and pain perception by mechanisms similar to those suggested in mouse models.

Psychosocial and behavioural factors may also play an important role in the reporting of disease. We have

explored 'illness behaviour' and found no evidence to suggest that individuals with soft tissue injuries are different from their healthy twin in their attitudes and beliefs (authors' unpublished data).

Whatever the underlying mechanisms, the genetic component to soft tissue injury is likely to be multifactorial. One might expect several genes rather than a single gene to be involved as our data suggest that there is no common genetic component to the two disorders explored in this study. To add to the complexity there are also likely to be site-specific gene-environment interactions. These interactions could explain the independent heritability of each disorder found in our study. Appreciating the nature of these gene-environment interactions is fundamental to our understanding of the pathology and management of these common upper limb disorders.

With regard to the method used in this study, the self-reporting questionnaire is open to the usual criticisms of ascertainment bias, validity of self-reporting and case definition. However, our data were consistent with other estimates of disease prevalence for frozen shoulder and tennis elbow that range from 10–30% in large population studies [1, 2]. We explored a randomly selected group to obtain an estimate of the recall of self-reporting by return of a second questionnaire and also assessed general practice notes for evidence of diagnosis. We did not find any significant differences between the study population and the recall or case note subgroups.

A more specific assessment of current disease may have helped to reduce bias in our study, improve concordance and possibly point towards particular mechanisms. However, agreement over case definition continues to cause concern in soft tissue research and, despite the development of new diagnostic pro formas [12], the definition of soft tissue pathology on clinical examination, particularly around the shoulder, remains difficult. Also, the reporting of past disease in our study was no more prone to the difficulties of a reliance on physician diagnosis than any other questionnaire-based survey. Given the prevalence of disease in this study was consistent with other population-based surveys, we feel the conclusions drawn are justified within the inherent restraints of the data.

In summary we have demonstrated a heritability of 42% in frozen shoulder and 40% in tennis elbow, and have shown that the genetic components to these heritabilities are independent for each disorder. The mechanisms, open to speculation at present, are likely to be multifactorial with gene-environment interactions that are site specific.

We have also shown a 2–3-fold increased risk of both disorders occurring in individuals. This risk is not mediated by common shared genetic or environmental factors but by individual-specific environmental factors.

Acknowledgements

AJH and AJM are supported by the Arthritis Research Campaign. The Twin Research Unit also receives support from the Wellcome Trust, the Chronic Disease Research Foundation and the British Heart Foundation.

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