Psoriasis and inflammatory arthritis coexist more often than would be expected by chance [1]. The evidence that psoriasis is an inherited disease is overwhelming. Family studies have shown up to 23% of first-degree relatives are affected, and twin studies reveal 70% of monozygotic twins are concordant [2].

Psoriatic arthritis (PsA) is a distinct entity with multiple patterns of joint involvement depending on which classification is used. The majority of patients with psoriasis who develop an arthritis similar to rheumatoid arthritis (RA) (approximately 75%) are rheumatoid factor (RF) negative [3], but it is uncertain whether psoriasis inhibits its production. RF positivity is low in the general psoriatic population. Enthesitis is more common in patients with PsA than in rheumatoid arthritis and is thought by some researchers to be the original site of inflammation in PsA [4, 5]. In some patients the symptoms related to enthesitis are more problematic than those from synovitis.

There are several distinguishing features which suggest that PsA is not identical to RA [4], for example:

(i) equal sex distribution,
(ii) predilection for distal interphalangeal joint involvement,
(iii) asymmetric distribution at presentation,
(iv) presence of spondyloarthritis in 40–50% of patients,
(v) association with HLA B27 antigen,
(vi) presence of enthesitis and dactylitis,
(vii) distinct radiological changes with asymmetrical joint damage and frequent involvement of the distal interphalangeal joints [Compared with RA there is often less periarticular osteoporosis, and more periosteal new bone formation. Extensive resorption of the distal ends of phalanges gives them a whittled appearance (in arthritis mutilans) and sacroiliitis with paraspinal ossification may occur alone or with any subtype of PsA. Evidence of enthesitis is easily detected by ultrasound.]
(viii) nail pitting and onycholysis,
(ix) histological differences [6].

There have previously been a number of small family studies describing the rate of various clinical features in the first-degree relatives (FDR) of probands with PsA but they did not report the concordance rate to the level of disease subtype. Baker et al. [7] found one definite and four probable cases of PsA in 47 FDR examined from 53 probands with PsA. Kammer et al. [8] found that 3% of 213 FDR had PsA. Moll and Wright [9] described 10 cases (12.5%) of PsA in FDR of 88 probands with PsA compared with no cases in FDR of probands with psoriasis and another form of arthritis. Finally, Gladman et al. [10] have recently described 46 cases of PsA (25%) in the siblings of 182 probands.

We were interested to measure the sibling concordance rate for arthritis and psoriasis as a measure of heritability. We also wished to establish whether the classification systems of joint involvement currently in use are valid: if there is an inherited risk of developing a particular pattern of PsA then one may observe affected siblings with similar patterns of arthritis. There is a lack of agreement about the currently used classifications of PsA; therefore the documentation of the pattern of disease in affected siblings may address these discrepancies in more detail and clarify whether any system is meaningful.
Methods

Patients

The Freeman Hospital rheumatology database was searched for prevalent cases of PsA (irrespective of RF status) with peripheral joint involvement. All available and consenting patients and consenting siblings within a 50 mile radius of Newcastle upon Tyne were assessed. Clinical documentation included extent of psoriasis (skin, nail and scalp involvement), presence of enthesitis [11] and synovitis, and pattern of joint involvement. Radiographs were not taken.

In patients with PsA the pattern of disease was classified according to Moll and Wright’s classification [12], with an additional category of ‘enthesitis alone’. The dually affected sibships were then distributed according to classifications suggested by Helliwell et al. [13], Veale et al. [14] and McGonagle et al. [15]. Patients with psoriasis were divided according to the onset of disease; type I disease, onset before age 40 yr and type II, onset after age 40 yr [16].

To eliminate interobserver bias, all subjects were assessed by A.M. Local Research Ethics Committee approval was obtained.

Calculation of concordance rates

Mean sibling concordance rate. Logistic regression analysis has suggested that the best predictor of concordance in a sibship is the size of the sibship, therefore the larger the sibship the greater the chance of concordance [17]. To eliminate this bias, a mean sibling concordance rate (MSCR) was calculated for each sibship.

Segregation analysis. Segregation analysis is when the observed proportion of affected siblings and offspring is compared with the proportion expected according to a particular genetic hypothesis. The method of analysis depends on the mode of ascertainment. For our study complete ascertainment, i.e. identification of all affected individuals in the community, was impossible. The simplest method of determining the proportion of affected siblings of probands is to count each sibship once for each time it has been independently ascertained, omitting the proband each time. This is referred to as Weinberg’s ‘proband’ method [18].

Familial aggregation and heritability

Familial aggregation. An index for expressing the degree of familial aggregation is the K factor [19]. This is the ratio between the observed prevalence in relatives and the expected prevalence in population controls. It does not give an indication of the mechanism of inheritance but indicates the importance of genetic factors. Any K value greater than 10 is regarded as a significant indicator of genetic determination.

Heritability. The heritability expresses the extent to which the phenotypes exhibited by parents are transmitted to their offspring. It therefore determines the magnitude of the correlation between relatives. Falconer [20] defined heritability as the additive genetic variance (attributable to the average affects of genes considered singly, as transmitted in the gametes) as a proportion of the phenotypic variance. If the heritability is very high the degree of genetic determination must also be high and the extent of environmental factors less so. Falconer devised a simple graph for estimating heritability from the prevalence in first-degree relatives and in the general population.

Results

Population

Eighty index cases and 112 siblings were assessed. The median age of index cases was 49 yr (range 24–80 yr) and for siblings 46 yr (range 18–79 yr). The median duration for psoriasis in the index cases was 18.5 yr (range 1–60 yr), and for psoriatic arthritis was 10 yr (range 1–54 yr).

In 79% of index cases, the onset of psoriasis preceded psoriatic arthritis by a median of 9 yr (range 1–55 yr). The onset of psoriasis before the age of 40 yr (i.e. type I psoriasis) occurred in 79% of index cases. No index cases were receiving biologic agents (i.e. etanercept or infliximab) at the time of the study. In the siblings psoriasis was present in 21% [median duration 26 yr (range 1–44 yr)].

There was a predominance of female siblings (70.5%) which was statistically significant ($\chi^2 = 4.9$, $P = 0.02$).

Concordance rates

The concordance rates, measured by MSCR and Weinberg’s proband method for psoriatic arthritis (using Moll and Wright’s classification) are shown in Table 1. The concordance of PsA, for all patterns including enthesitis, was 14.6% (MSCR) and 13.4% (Weinberg’s method). If enthesitis was excluded then the concordance rates are 9% and 8.3% respectively.

The concordance rates for the type of psoriasis as defined by age of onset, i.e. type I psoriasis is when onset occurs before the age of 40 yr, are 17.7% (MSCR) and 19.5% (Weinberg’s method).

We found 6% of index cases had RF greater than 1:80 titre (not significantly different from the general population) and approximately 5% of siblings had a positive titre. If those index cases with a positive RF were excluded from the analysis, no difference was found by the two methods of measuring concordance rates for PsA.

Familial aggregation and heritability

In our sibling study we have calculated a frequency of PsA in siblings 47 times that found in local population controls ($K = 47$) [22]. Familial aggregation of psoriasis was 12 times higher in siblings compared with population controls ($K = 12$).

The heritability expresses the extent to which the phenotypes exhibited by parents are transmitted to their offspring. It therefore determines the magnitude of the correlation between relatives. Using Falconer’s simple graph [20] for estimating heritability from the prevalence in first-degree relatives and in the general population, the heritability score for PsA is greater than 100%, indicating high heritability. The heritability for PsA is greater than in autoimmune conditions such as RA, primary Sjögren’s syndrome and thyroid disease (Table 2).

Table 1. Concordance rates for psoriatic arthritis in the siblings

<table>
<thead>
<tr>
<th>Moll and Wright subtype</th>
<th>Index case (%)</th>
<th>MSCR (%)</th>
<th>Weinberg’s proband method (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically indistinguishable from RA</td>
<td>55</td>
<td>3.2/80 (4%)</td>
<td>5/118 (4.2%)</td>
</tr>
<tr>
<td>Oligoarticular</td>
<td>20</td>
<td>2.5/80 (3%)</td>
<td>3/118 (2.5%)</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>15</td>
<td>1.8/80 (1%)</td>
<td>1/118 (0.8%)</td>
</tr>
<tr>
<td>Arthritis mutilans</td>
<td>–</td>
<td>1.8/80 (1%)</td>
<td>1/118 (0.8%)</td>
</tr>
<tr>
<td>Distal interphalangeal joint</td>
<td>9</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>1</td>
<td>4.5/80 (5.6%)</td>
<td>6/118 (5.1%)</td>
</tr>
</tbody>
</table>
Table 2. Heritability scores in PsA compared with primary Sjögren’s syndrome, RA and thyroid disease (%)

<table>
<thead>
<tr>
<th></th>
<th>FDR</th>
<th>General population</th>
<th>Heritability score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PsA</td>
<td>14</td>
<td>0.3</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Primary Sjögren’s</td>
<td>4.4a</td>
<td>2.7b</td>
<td>80–90</td>
</tr>
<tr>
<td>RA</td>
<td>5.3c</td>
<td>~1d</td>
<td>60</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>11.4e</td>
<td>1.9e</td>
<td>70</td>
</tr>
</tbody>
</table>

Previously published data: aFoster [30]; bJacobsen et al. [31]; cDeighton [21]; dLawrence [32]; eTunbridge et al. [33].

Recurrence of different patterns of arthritis

Four of the 16 sibships (25%) had the same pattern of joint involvement (Moll and Wright classification). The most frequently occurring was joint involvement clinically identical to rheumatoid arthritis (3/4). There were nine sibships (56%) in which synovitis of a different pattern to the index case occurred, i.e. rheumatoid, oligoarticular or mutilans patterns. Finally, in seven sibships (44%), the pattern of disease was predominantly enthesitic.

When the dually affected sibships were analysed using Helliwell et al.’s [13] and McGonagle et al.’s [15] classifications, 10/16 (62.5%) of dually affected sibships had the same pattern of PsA, compared with 4/16 (25%) of sibships with Veale et al.’s classification [14].

Discussion

This is the first study to investigate sibling concordance rates for PsA and psoriasis. Our study reveals a concordance rate for all patterns of PsA of approximately 14% including enthesitis, and 9% for involvement of synovial joints. This is similar to that previously documented in HLA-identical siblings of index cases with RA (15%) [21]. Local data have revealed a point prevalence of involvement of synovial joints. This is similar to that previously published studies (9% compared with 5.5% [9]) and significantly higher than the local background population.

We are unable to make comparisons with other studies with regard to the subtypes of PsA because the data were not reported at this level in other studies. Few sibships were concordant for disease pattern (Moll and Wright), which suggests that the underlying predisposition for arthritis inherited with psoriasis is for synovitis/enthesitis and not for a specific disease pattern using the current most popular classification [12]. However, as we now know that disease pattern may not stay the same over time [29] and most siblings are discordant there may be no benefit in using the classification systems currently available. The lack of X-rays in our study may have led to some misclassification of subjects, but this is likely to have been small.

Reassuringly there was no difference between the two methods used to calculate concordance rates (using Moll and Wright’s classification) in this study, thus allowing comparisons to be made with any studies published in the future whichever system is used. However it must be remembered that most of the sibships studied included only two siblings, which limits the interpretation of this data.

Using different classifications for disease patterns in PsA we have found different concordance of type of disease within dually affected sibships. The most commonly used classification (Moll and Wright [12]) reveals that four of the 16 sibships have the same pattern of joint involvement, the most frequently occurring is joint involvement clinically similar to RA (approximately 4%). However, when other proposed classifications, which are simpler, were used (Helliwell et al. [13] and McGonagle et al. [15]), there were higher levels of same-pattern dually affected sibships (62.5%). This was not confirmed when Veale et al.’s [14] classification was used. Clearly the fewer diagnostic groups used, the greater the random chance of concordance.

There was considerable overlap between the various subgroups of current PsA classifications and with the observation that joint pattern can change over time [29]; this suggests there is a common underlying factor. However, until this sibship study it has not been possible to demonstrate the discrepancies between currently available classifications and it has also demonstrated the difficulties clinicians have in differentiating the subtypes of PsA. This study further highlights the need for an international effort to develop validated classification criteria for PsA.

Finally in siblings of probands with PsA, the degree of familial aggregation (K) of PsA was high when compared with local population controls. These results are comparable with those published by Moll and Wright [9], suggesting a significant index of genetic determination for PsA supported by high heritability scores. This result would be artificially elevated if the families assessed showed a Mendelian pattern of inheritance, but careful scrutiny of our pedigrees failed to reveal any clear pattern. The heritability for PsA is greater than in autoimmune conditions such as RA [21], primary Sjögren’s syndrome [30] and thyroid disease [33].
In summary, we have shown a sibling concordance rate for psoriatic arthritis of 14% (9% for synovial disease alone) and for psoriasis of 21%. The concordance for psoriasis is similar to published studies but there is a higher concordance of psoriatic arthritis in our siblings compared with previously published family studies. The heritability for PsA appears greater than for RA, but consideration must be given to environmental factors, which could be important in precipitating PsA in genetically susceptible individuals.

The authors have declared no conflicts of interest.

References