A family study of Behcet’s syndrome

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Summary The first-degree family members of patients with Behcet’s syndrome were investigated to determine (1) whether there was a familial aggregation of Behcet’s syndrome or of its component features, (2) whether there was an increased incidence of sacro-ililitis in these families, and (3) whether a link exists between Behcet’s syndrome and spondarthritides in first-degree relatives.

Of the 226 relatives and patients seen, 21 patients with definite Behcet’s syndrome and their 71 relatives were analysed in some detail. Orogenital ulceration was found in 2 mothers of probands; 1 patient had psoriasis and Behcet’s but neither disease featured in the pedigree. Another family showed numerous manifestations of psoriasis and psoriatic arthritis, 1 member having severe sacro-ililitis but the proband had Behcet’s syndrome only. Family trees including HLA pedigrees, where known, are presented.

Spouses suffered few of the complaints found in patients, and to a less extent in relatives, but showed a high incidence of backache, perhaps of psychogenic origin.

Classical Behcet’s syndrome is relatively easy to recognise because of the triad of features—mouth ulceration, genital ulceration, and iritis. Less complete cases are more difficult and this has led some authors to propose criteria which have to be satisfied at various levels to give the diagnostic categories of definite and possible Behcet’s syndrome (Mason and Barnes, 1969). One of the minor criteria used in their series is the family history of the disorder, and the authors give 4 pedigrees in which features occur in first-degree relatives.

Familial involvement has been repeatedly but infrequently reported (Forbes and Robson, 1960; Fowler et al., 1968). However, while there is a report from Japan of the incidence of the disease itself (Aoki and Katsumata, 1971), there appears to be no information on the prevalence of the disease, or of some of its features, in relatives. The present survey was designed to provide some information on the prevalence of the syndrome in first-degree relatives in a circumscribed area, the (old) county of Yorkshire with a population of approximately 5 million.

It has been postulated (Wright and Watkinson, 1965; Wright, 1966) that there are linkages between certain bowel disorders such as ulcerative colitis, Crohn’s disease, and ankyllosing spondylitis and between ankylosing spondylitis, psoriasis, Reiter’s disease, and possibly Behcet’s syndrome. The group of diseases have been named seronegative spondarthritides (Wright and Moll, 1976).

The survey was thus mounted with the following aims: (1) To investigate whether there was a familial aggregation of Behcet’s syndrome or its component features. (2) To determine the prevalence of sacro-ililitis in these families. (3) To investigate a possible link between Behcet’s syndrome and spondarthritides in first-degree relatives.

Material and methods

Thirty-two patients were interviewed and examined as outlined previously (Chamberlain, 1978), the method being substantially that outlined by Moll (1971). Two hundred and twenty-six relatives and spouses were named by patients: those that lived in Yorkshire, with easy access to Leeds, York, or Sheffield were asked to attend for interview; those that were available but living at a greater distance were asked to attend their local hospital for x-rays of the hands, feet, and sacro-iliac joints (subject to restrictions laid down by the MRC, that no asymptomatic pre-menopausal women and no males under the age of 15 years had a pelvic radiograph). The interview and examination (results of which were recorded in a detailed proforma) were supplemented by immunological studies and histocompatibility antigen determinations whenever possible.

Data were analysed conventionally and by q-analysis (Atkin, 1974; Chamberlain, 1976). Q-analysis provides a study of the connectivities (the relationships existing) between members of a set Y.
when these are related (via a mathematical relation) to another set X. These connectivities characterise the simplicial complex KY (X;λ) defined by λ; similarly the relation λ⁻¹ gives the complex KX (Y;λ⁻¹) in which are exhibited the connectivities between members of X (as they are more or less shared members of Y). In the context of this study the sets were: Y = (names of individual people), X = (names of disease attributes) with the understanding that the sets were 'hierarchically pure'.

Data presented here are largely derived from the families of 21 patients with definite Behçet's disease (Mason and Barnes, 1969) in an attempt to concentrate and highlight any positive findings. They do not differ fundamentally from the findings on the whole group of 32 patients and their relatives. Pedigrees for all families in which mouth ulceration occurs in members other than the patient are given with tissue typing where available.

Results

Of the 226 relatives named by patients, 92 were not available for study (living out of the area or abroad, serving in HM forces or, and occasionally being deemed too ill or old). Of 134 contacted 89 were interviewed, 3 returned a simple questionnaire (and were X-rayed) and a total of 17 had radiographs at their local hospital. The completion rate was thus 81%.

The 21 patients with definite Behçet's syndrome had 71 relatives available for interview. The group consisted of 4 fathers, 10 mothers, 7 brothers and 10 sisters, and 15 sons and 11 daughters. There were 9 husbands and 5 wives acting as controls. A further 10 subjects were X-rayed only.

Mouth ulceration was only regarded as 'significant' when it occurred more than annually, when more than one ulcer was present simultaneously, and when those ulcers were at least 1 cm in diameter and not entirely superficial. The ulcers of Behçet's extend into the fauces and when this was present it was noted. Three mothers, 3 sons, and 2 daughters in the 'definite' subgroup had 'significant' oral ulcers, giving a prevalence of 11.3%. One further mother of a 'possible' Behçet's subject and 1 daughter also had 'significant' mouth ulcers.

Pedigrees are shown in Figs. 1–5 and the severity of individual patient's stomatitis is detailed. In general, this rarely reached the severity found in probands but it often started at a similarly early age.

Stomatitis was never found in spouses, fathers, or siblings.

Genital ulceration was present in 2 mothers only, both of whom had mouth ulcers. In the first, the mother's and daughter's genital ulceration was contemporaneous with mouth ulceration and associated with skin sepsis and acne. In the second mother, small red areas on the labia broke down and were associated with vaginal soreness and bleeding without gross ulceration.

Genital ulceration was never found in spouses.

Iritis, sepsis on pin prick, erythema nodosum and serious central nervous system lesions were not experienced by relatives or spouses.

Acne was present in 1 mother.

Thrombosis was present in 1 female spouse with no other symptoms, and in 1 mother who had mouth ulcers.

Arthritis

The non-destructive, nodular synovitis of Behçet's was not found in any relative or spouses. One mother had rheumatoid arthritis, 1 father had gout, and 4 had osteoarthrosis (1 spouse, 2 mothers, 1 son).

Psoriasis and psoriatic arthropathy

One patient had psoriasis and Behçet's syndrome. The interviewed members of his family were not affected by either. Psoriasis was found in family 17 (see Fig. 6). The proband's father had psoriasis, psoriatic arthritis, sacro-iliitis, and a raised IgA; the sister had polyarthralgia and psoriasis; and 1 brother a single episode of arthritis.

Lumbar pain lasting more than 2 weeks was found in 5 spouses, 1 father, 4 mothers, and 4 siblings. In no case was it associated with any restriction of lumbar movement. Similarly, although 4 subjects were found with restriction of lumbar movement, these subjects did not suffer persistent back pain and restriction of movement only occurred in 2 of the possible directions (forward flexion, lateral rotation to left and right).

Gastrointestinal diseases associated with spondylitis and arthritis such as Crohn's disease or ulcerative colitis were not found.

Sacro-iliitis

The incidence in probands and first-degree relatives is shown in the Table. Thirty-seven relatives were X-rayed. The father with psoriasis already referred to had Grade 4 sacro-iliitis. Another proband's mother had Grade 2 sacro-iliitis (without lumbar pain or restricted movement), osteoarthrosis of the knees, and Heberden's nodes.
Table

<table>
<thead>
<tr>
<th>Interviewed subjects</th>
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<tr>
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<tr>
<td>Total (relatives)</td>
<td>2</td>
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*See Fig. 6 (psoriatic family)
†Osteoarthrosis of knees and Heberden's nodes.

Immunology

The sheep cell agglutination titre was positive in 2 husbands without rheumatoid arthritis and in 1 mother with this diagnosis.

Significantly raised levels of IgA were found in 3% relatives, 0% spouses, and 0% patients with Behcet's. Similarly, significantly raised levels of IgM were present in 6% relatives and 9% spouses (compared with 11% patients with Behcet's syndrome).

Evidence from q-analysis substantiates the above findings. It confirms that mouth ulceration and genital ulceration are linked both among the patients and occasionally amongst the relatives and that both are absent from the spouse data. It confirms that in probands certain features such as arthritis, phlebitis, erythema nodosum, and the Blobner phenomenon are closely related to orogenital ulceration and to the disease but that these features occurring in isolation have no diagnostic value and are often attributes of other diseases. Similarly, those features which are highly associated with serious Behcet's disease (iritis, erythema nodosum, vasculitis) occur only rarely in the relatives and are totally absent from the spouses.

Features associated with psoriasis (backache, sacro-iliitis, psoriatic arthritis, raised IgA) are connected together amongst relatives and show a familial aggregation but are dissociated from mouth ulceration and genital ulceration.

Backache is a prominent feature of spouses whether male or female, with or without sciatica. The clustering of disease features in spouses is totally unlike that found in probands. The position of relatives is intermediate.

Pedigrees of Families

The prevalence of HLA-B5 in the Behcet's disease (including further patients not in the family study) is 17.9%. This breaks down to a prevalence amongst females of nil (compared with prevalence of 9.1% among control females) and among males of 41.7%.

Four male patients in the series were B5 positive of whom 1 had uveitis and a total of 3 had definite Behcet's disease. The pedigree of 1 family in whom other members were tissue typed is shown (Fig. 1)*. No members of this family carried the B5 gene and none had complaints. Other incomplete pedigrees were available but unhelpful. Only those in which mouth ulceration occurred in subjects other than the proband will be discussed here.

![Family 9](image)

Fig. 1

Family 26 (Fig. 2)

![Family 26](image)

The proband (II.2) was a young boy aged 8 years. He had had severe mouth ulceration since the age of 5 years and genital ulceration since 6 years. He also had septic skin lesions and an episode of arthritis of the knees at the age of 3.

The father (I.1) was reported as well.

*Where tissue typing was done this is shown in the various pedigrees. Thus case II. 1, Fig. 1:— 2, 9

12, ?
The mother (I.2) aged 33, had mouth ulceration which began at the age of 13, recurring never less than 3 times a year, at least 3 ulcers occurring at once. The ulcers were as deep as her son's extending into the fauces and resulting in scarring.

Genital involvement began at the age of 28 years. Raised red areas on the labia occurred simultaneously with mouth ulceration, bled and broke down. Bleeding and vaginal discharge without vaginal ulceration, had been reported.

The patient's brother (II.1, aged 11) had occasional insignificant mouth ulceration.

His maternal aunt (I.3) had had back pain and mouth ulceration.

**Family 5 (Fig. 3)**

- The proband (II.2) was a married woman aged 33 years. She suffered from definite Behçet's disease. Mouth ulceration began at the age of 9 and genital ulceration followed 7 years later. Mouth ulcers were frequent, deep, and extensive, leaving tongue scarring; oral steroids were used to try to diminish symptoms. The Blobner phenomenon was present and phlebitis, an aryttenoid ulcer, and probably also erythema nodosum occurred. B27 and B5 were not present.

- Her father (I.1) had died of cancer, the mother (I.2) was alive, complaining of mouth ulceration occurring 1 to 3 times a year in crops of up to 3 ulcers which were very painful. She had also had eczema, recurrent conjunctivitis, thrombosed veins, a single transient episode of knee pain due to 'cartilage' and 2 coronary thromboses.

- The patient's brother (II.3, aged 29) was entirely normal. The patient had two sons, aged 11 and 8 years (III.1, III.2) at interview. Both got ulcers 'like their mother'. The older boy's ulcers began at the age of 7, occurred at least 3 times a year in crops of up to 3 ulcers on any one occasion. They were bigger than the father's but smaller than the mother's occurring on the inside of the cheek but sparing the fauces and the tongue.

The younger boy's ulcers began at the age of 5, with similar frequency, duration, site, and number. Neither B27 nor B5 was present.

The husband (II.1) was symptom free apart from occasional mouth ulcers, the size of a pinhead.

**Family 6 (Fig. 4)**

The proband (II.1) was a man of 50 years with severe Behçet's disease of 10 years' standing. He had severe mouth and throat ulceration, genital ulceration, acne, skin sepsis, and arthritis.

His daughter (III.1, aged 27 years) had mouth ulcers which began at the age of 15 years, occurring as often as 3 times a year with up to 3 ulcers present on any one occasion. These lasted 10 days were 0.5–1 cm in diameter, painful but not deep, and were of debatable significance.

His wife (II.2) had lumbar pain and osteoarthritis.

**Family 14 (Fig. 5)**
This family is interesting, the proband (II.1) being a 19-year old girl with definite Behcet's disease who first had mouth ulcers at the age of 8 years. Ulcers occurred more than 3 times a year, at least 3 ulcers being present at a time, though not spreading into the fauces. Genital ulceration also began at the age of 8 years and was associated with mouth ulceration. Acne, skin sepsis, perianal pustules, and a deep vein thrombosis had occurred together with ulceration of the epiglottic fold.

No information was available about the father (I.1).

The mother (I.2) first experienced mouth ulceration at an early age (19 years). She had at least 3 ulcers on each occasion which extended from the lower lip to the throat, making swallowing painful. They were as large as a thumb nail, lasted 2 weeks, and occurred at least 3 times a year with scarring. She suffered from acne and had 1 episode of arthritis of the ankles at the age of 16 years (3 years before mouth ulceration).

The patient had a 9-year old sister (II.2) with insignificant mouth ulceration, and another normal sister (II.3) aged 6.

Only the patient had been tissue typed. She was 2, 12.

II, 15

Family 17 (Fig. 6)

Family 17

1

2

1, 1, 2

1, 2 or x

7, 7 W17

13, 10

3, 10

HLA antigens not tested

4

2, 9

7, 7 W22

III

1

2

1, 1

7, 13

HLA antigens not tested

3

HLA antigens not tested

The proband (II.1) was aged 32 years. Definite Behcet's disease began with mouth ulceration at the age of 21 years after the birth of her first child. Genital ulceration followed 5 years later but although frequent and severe was not coincidental with mouth ulceration (which had the features documented in the other probands). Sepsis resulted from skin pricks. There had been severe emotional problems, leading to attempted suicide and recently a right hemicolectomy had been performed for non-specific caecal ulceration.

The father (I.1, aged 70) had psoriasis, psoriatic arthritis, grade 4 sacro-ililitis, and bronchitis.

The mother (I.2, aged 65) suffered from recurrent lumbosacral pain.

The patient had a sister (II.4, aged 26 years) who had psoriasis and backache. She had had 1 episode of polyarthritis lasting a few weeks (SCAT–ve).

The brother (II.3, aged 28 years) had had 1 episode of shoulder and MCP pain associated with trauma.

There were 3 children of the marriage. A daughter (III.2, aged 7 years) and 1 son (III.3, aged 6) were symptomless. A son (III.1, aged 10) had mouth ulceration which began at the age of 7 years, occurring as often as 6 times a year with up to 3 painful ulcers at a time. These lasted up to 10 days and were found inside the lips. They were as big but not as deep as his mother's.

The patient's husband, aged 32 years (II.2) was symptom free.

Discussion

Berlin (1960) documented a brother and a sister with Behcet's syndrome, the sister developing the illness 5 years after her brother's death. He also stated that according to his knowledge no man to wife transmission was observed although the areas of the body are affected where the possibility of infection is greatest. Fadli and Yousef (1973) stated 'in three incidences we get two siblings showing the disease simultaneously, i.e. three families out of 20 (16%).'

Forbes and Robson (1960), Fowler et al. (1968), and Mason and Barnes (1969) also noted a familial incidence but these studies are difficult to interpret since often the individual symptoms are not stated. All fall into the first of the 4 types of studies listed by Masi and Shulman (1965) viz., (1) isolated kindreds, (2) prevalence among relatives of affected index cases, (3) population studies, (4) concordance in twins. The present study falls into class (2) and mouth ulceration (sometimes with genital ulceration) occurred in first-degree relatives. Although the numbers are small and do not achieve statistical significance, recurrent aphthosis may be the backcloth on which Behcet's syndrome emerges. Features normally closely associated with Behcet's such as erythema nodosum and arthritis were not found in relatives. None of the family members developed sepsis on pin-prick. Thrombosis presented no more commonly in the relatives than the controls but this rare feature occurred together in this series, ie, in a proband and his sister.
Although these negative findings are not in doubt, caution has to be exercised in interpreting positive findings (see Bennett and Wood, 1968); the interview method tends to boost the number of cases of disease in question and a subject with disease more readily identifies others in his family who might have that disease. It is also difficult to provide strict comparability of the environment of test subjects and controls, for although spouse controls live at the same address as probands one cannot assume that the working environment was or is similar. Finally, in long term disease, features tend to become blurred.

One may speculate about the high prevalence of lumbar pain in spouses and perhaps conclude that this is related to the anxiety and depression the husband and wife suffer and the often unspoken fear of the disease being venereal.

HLA-B5 has been found to be more common in Japanese patients than in controls (Ohni et al., 1973). Figures from England (Jung, et al., 1976) and America (O'Duffy et al., 1976) are at variance with this. The frequency of B5 differs in Caucasian and Japanese control populations. The overall prevalence of B5 is not raised in the whole group of probands in the present study but there is a marked difference in frequency when the 2 sexes are separated, the level of B5 in males (41.7%) becoming significant. This sex difference has not been reported before.

Pedigree studies are limited in this series, but HLA-B5 does not feature in these families with mouth ulcers and does not appear to be associated with uveitis in probands. HLA-B27 was found with slightly increased frequency in both sexes in the probands on which the present study is based (significance being abolished if one takes account of the number of histocompatibility antigens).

Wright and Watkinson (1965) and Wright (1966) postulated that Behcet's disease might be related to the seronegative spondarthritides. Indeed there are several reports of bowel ulceration and even of ulcerative colitis occurring in probands (Boe et al., 1958; Empey and Hale, 1972). There appears to be little in the literature about the relationship between Behcet's disease in probands and these disorders in their families. No cases of bowel involvement were found in the present survey, but 1 family with psoriasis was found.

The frequency of sacro-iliitis in the families of probands in this series was 5.5% overall (including spouses) but 11% for first-degree relatives. One of these 2 subjects had psoriatic arthritis with associated features. The expected incidence of sacro-iliitis would be 1-1% (Moll, 1971) but with the finding of only 2 cases of sacro-iliitis it is difficult to interpret.

The survey suggests that familial and genetic factors may have a modest part to play in the development of Behcet's disease in a predominantly Caucasian population in a developed country. The importance of environmental and inherited factors may well be different in other situations (in Japan and the Middle East, for example). The relationship between the disease itself and orogenital ulceration and aphthous ulceration in relatives does not reach statistical significance in this small series but it is interesting that these 2 features without which diagnosis of Behcet's syndrome should rarely be made, penetrate into first degree relatives.

Conclusions

First-degree relatives of patients with definite Behcet's syndrome occasionally suffered from mouth and, less commonly, genital ulceration, but not from uveitis and other features of severe disease. The ulceration are of the same type as the patient's but rarely of the same severity. They were not found in the spouses who served as controls.

Sacro-iliitis probably did not occur with increased frequency in the small number of probands or their relatives.

The analysis suggests that neither psoriasis nor psoriatic arthropathy are related to Behcet's even though one family with both psoriasis and Behcet's syndrome was encountered. The clinical features of the former separate out from the Behcet's features. There appears to be no increased prevalence of spondarthritides in these families. The high incidence of HLA-B5 in male probands in this series remains to be explained. It is not correlated with the features found in severe disease in this series or with families in whom mouth and genital ulceration appear in more than 1 member.

If inheritance plays any part in providing a backdrop for the development of Behcet's syndrome, it is limited to a tendency to produce orogenital ulceration. Similarly, because of the absence of clinical features in spouses, infectivity of the order seen in childhood exanthemata is unlikely to be of importance.

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