LETTERS TO THE EDITOR

Behçet disease: advantageous against development of neoplasia?

Although a good deal is known about the late occurrence of malignancy in the connective tissue disorders and other vasculitides, including the autoimmune diseases, for example, rheumatoid arthritis, progressive systemic sclerosis, Sjögren syndrome, systemic lupus erythematosus, and so on,¹ there have been few reports on concurrent neoplasms in Behçet disease and all of these were devoid of any documented pathophysiology except for the possibility of a drug induced relationship.²⁻⁵

In our referral teaching hospital, over 400 Behçet disease patients have been followed in the last 15 years on single agent and/or combined treatment protocols consisting of non-steroidal anti-inflammatory drugs, corticosteroids, colchicine, and occasionally azathioprine (required in less than 1%). The median follow up duration for our patients is 9.8 years (range 1.2 to 15+ years) and no patients have been lost to follow up. In spite of the frequent controls and various treatment methods used in our several randomised trials for the management of Behçet disease and its related vasculitic complications, we noticed the absence of de novo or drug related malignancy in any of the cases during the long term follow up.

Behçet disease is a syndrome complex of chronic relapsing vasculitis where the precise underlying pathogenic mechanism is not clear. Though not universal, the strong association of Behçet disease with HLA-B5 in several ethnic groups is well described,

which suggests an HLA related immunopathogenic explanation.⁶ Also, the presence of HLA-B5 in Behçet disease contrasts with other autoimmune conditions and collagen vascular diseases in that it has the unique feature of being unrelated to HLA-A, C, D, or DR antigens. Thus this specific antigenic determinant of Behçet disease forms a unique clinical picture characterised by antibody formation restricted only to certain local conditions secondary to vasculitic endothelial injury, with absence of systemic derangements in the immune system. In addition, large patient series from various countries do not suggest there is a link between Behçet disease and particular collagen vascular diseases^{7,8} and this might further contribute to the lowered incidence of neoplasia in these individuals.

Behçet disease shows a wide spectrum of presentations which vary among different races, and this observation in our particular ethnic group needs to be confirmed in others. As no specific gene rearrangement or evidence of a tumour-suppressor gene have yet been described as a possible explanation, it remains to be determined through further study whether Behçet disease patients are lucky in possessing a protective HLA subtype against malignant transformation.

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Parvovirus B19 and acute joint swelling in rheumatoid arthritis patients

Human parvovirus B19 is the aetiological agent of erythema infectiosum and transient aplastic crisis in patients with shortened red cell survival.¹ Joint symptoms associated with B19 infection occur in up to 80% of infected adults, and usually occur symmetrically in the hands, wrists, knees, and cervical spine.¹ Arthralgia is usually acute and self limiting, but may be chronic and recurrent. Most patients with these symptoms are women^{2,3} and rheumatoid factor may be present or rise following B19 infection.³ In these patients, the 1987 American Rheumatism Association criteria for diagnosis of rheumatoid arthritis are often met. Although B19 DNA has been demonstrated in synovial fluid,⁴ synovial fluid cells,⁵ and synovial tissue,⁶ the evidence for the role of B19 in the causation of rheumatoid arthritis has been conflicting. We hypothesised that if persistent B19 infection triggers a chronic polyarthritis identical to rheumatoid arthritis, then patients with rheumatoid arthritis may, at the time of acute joint swelling, have B19 DNA in the serum, synovial fluid, and synovial fluid cells significantly more often than controls.

Twenty nine patients with acute joint swelling requiring knee joint aspiration were assessed: 18 test patients had rheumatoid arthritis, and 11 control patients had nonrheumatoid (non-RA) disease. Among the rheumatoid arthritis group (patients 1-18), the female to male ratio was 2:1 and the age range was 13-72 years, with a mean of 53.7 years. Duration of rheumatoid disease ranged from two to 30 years with a mean of 12.9 years. Among the non-RA group (patients 19-29), the female to male ratio was 7:4 and the age range was 15 to 83 years, with a mean of 52 years (table).

Ten millilitres of both synovial fluid and serum were taken from each patient. C reactive protein was measured in serum using laser nephelometry. Anti-B19 IgM and IgG were assayed in serum and synovial fluid by a fluorescent antibody technique as described previously.⁷ Hyaluronidase was added to synovial fluid (100 IU ml⁻¹), and synovial fluid cells were pelleted by centrifugation at 400 g and separated from the supernatant. DNA was obtained from serum and synovial

Patients details and results of serum and synovial fluid testing

Patient number	Age (years)	Sex	Diagnosis*	Duration of disease (years)	C reactive protein (mg l ⁻¹)	Serum B19 IgG	Synovial fluid B19 IgG
1	54	F	RA	16	1.6	+	+
2	62	F	RA	17	< 0.99	+	-
3	72	F	RA	5	98.5	-	-
4	56	M	RA	20	12.1	-	-
5	43	M	RA	9	43.5	+	+
6	58	M	RA	10	67.2	+	-
7	72	F	RA	20	17.0	+	+
8	45	F	RA	17	37.1	+	+
9	52	F	RA	12	99.5	+	-
10	62	F	RA	13	73.2	+	-
11	63	F	RA	8	17.0	+	+
12	48	M	RA	2	21.3	+	-
13	72	F	RA	5	97.0	+	+
14	68	F	RA	30	82.5	+	+
15	56	F	RA	18	2.79	-	-
16	56	M	RA	-	11.1	-	-
17	13	F	RA	-	1.41	+	+
18	14	M	RA	4	10.6	+	+
19	61	M	OA	-	57.7	+	+
20	83	F	OA	-	< 0.99	-	-
21	66	F	OA	-	< 0.99	-	-
22	72	F	OA	-	1.69	+	+
23	68	F	OA	-	3.28	+	-
24	80	F	OA	-	2.47	+	+
25	27	M	Psor	-	91.3	+	+
26	45	F	Psor	-	23.7	-	-
27	36	M	Psor	-	5.69	+	+
28	18	F	Reactive	-	101.	+	+
29	15	M	Reiter	-	73.3	+	+

*RA, rheumatoid arthritis; OA, osteoarthritis; Psor, psoriatic arthritis; Reiter, Reiter syndrome.

fluid by phenol/chloroform extraction. DNA was obtained from synovial fluid cells by homogenisation in TRI reagent (Molecular Research Centre, Cincinnati, Ohio, USA). DNA extracts were stored at -80°C . DNA extracts were tested for B19 DNA by a nested PCR assay.⁸ DNA extracts from positive (viraemic) and negative control sera were included in each run.

The C reactive protein was above 10 mg litre⁻¹ in all but four rheumatoid arthritis patients, providing evidence of rheumatoid disease activity (table). In serum, 14 of 18 rheumatoid arthritis patients (77%) and eight of 11 non-RA patients (73%) were positive for anti-B19 IgG (table). In synovial fluid, nine of 18 rheumatoid arthritis patients (50%) and seven of 11 non-RA patients (64%) were positive for anti-B19 IgG (table). Serum and synovial fluid from all patients from both groups were anti-B19 IgM negative. Serum, synovial fluid, and synovial fluid cells from all patients tested negative for serum B19 DNA.

Nikkari *et al*⁹ found serological evidence of recent parvoviral infection in four of 135 rheumatoid arthritis patients and two of 62 controls. No evidence for the presence of B19 DNA was found in 18 synovial fluids, 21 samples of synovial fluid granulocytes, and 40 sera, all obtained from 65 patients with early rheumatoid arthritis. Results of the present study—in which B19 DNA was not detected in serum, synovial fluid, or synovial fluid cells of either rheumatoid arthritis or non-RA patients—are consistent with those of Nikkari. The PCR sensitivity of the present study was of the order of 10–100 genome copies per ml¹⁰ and is comparable to that of Nikkari.⁹ Although not part of the present study, B19 DNA has been found in rheumatoid synovia.^{6–10} However, results of these studies are conflicting^{6–10} and it may be that B19 viraemia frequently leads to persistence in synovial macrophages.¹⁰

In conclusion, from the data obtained in this study, a role for B19 in the pathogenesis of acute joint swelling in rheumatoid arthritis patients was not supported.

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Down syndrome with coexistent gout: report of six patients and possible reasons for the scarcity of descriptions of this association

Although the association between Down syndrome and hyperuricaemia is well known,^{1,2} gouty arthritis has rarely been encountered in Down syndrome regardless of persistent hyperuricaemia.³ To date, there have been only scattered reports on five Down syndrome patients with coexistent gout^{4–7}; in this report we describe six such patients.

The table summarises the data in our six patients. Important data not included in the table are as follows: the maternal grandfather of case 1 had suffered from severe gout; case 2 was extremely obese (body mass index 33.1); case 3 had a patent arterial duct and pulmonary hypertension and had severe polycythaemia, presumably resulting from the cardiovascular abnormality; although case 5 had a ventricular septal defect and

pulmonary stenosis, the laboratory test showed no polycythaemia.

The diagnosis of gouty arthritis was made by demonstrating crystals in the joint fluid in one patient (case 1), while that for the other five patients was performed according to the American Rheumatism Association preliminary criteria for the classification of acute gouty arthritis.⁸

The six patients in the present report had large joint arthritis as the first gouty symptoms, although in general approximately 70% of gouty patients are believed to have great toe arthritis as the first symptom. This tendency was also observed—though less markedly—in the previous reports on the five patients cited above. Thus only in the two cases reported by Ciompi *et al* were the first joints involved great toes.⁶ The tendency of gouty arthritis to occur in large joints in Down syndrome patients remains to be explained. In five of our patients, 24 hour uric acid excretion was relatively low (table). Whether this tendency is a characteristic of Down syndrome patients should be examined in later studies.

The pretreatment serum urate concentrations of our six Down syndrome patients were not only higher than the age matched male Down syndrome controls but also higher than age matched male gout patients and control male gouty patients (figure). These data may indicate that the occurrence of gouty arthritis is suppressed in Down syndrome patients. One explanation could be that leucocyte function, which is necessary to cause gouty arthritis, is reported to be impaired in Down syndrome patients.⁹

The mean age of onset of arthritis in our six Down syndrome patients (23.0 years, SD 6.4) was significantly lower ($P<0.001$) than the control male gouty patients (43.2 years, SD 11.8, $n=350$). In the five patients described in published reports,^{4–7} the age of onset of arthritis (21.6 years, SD 4.9) in the Down syndrome patients with coexistent gout was also younger than general gouty patients. The earlier onset of gouty arthritis

Pretreatment serum urate concentrations in Down syndrome patients coexistent with gout (Down + gout, age 23.0 years, SD 6.4), age matched male Down syndrome patients (Age matched Down, age 23.0 years, SD 5.3), age matched male gout patients (Age matched gout, age 23.2 years, SD 9.6), and male gouty patients (Gout, age 43.2 years, SD 11.8). Error bars are SD.