**Case report**

**Neonatal Behçet’s syndrome in an infant of a mother with the disease**

ADEL G. FAM, KATHERINE A. SIMINOVITCH, SIMON CARETTE, AND LYNN FROM

*From the Rheumatic Disease Unit, Sunnybrook Medical Centre, University of Toronto, Toronto, Ontario, Canada*

**Summary** Behçet’s disease is reported in a newborn infant of a mother with the disease. The mother had recurrent orogenital ulcers, pustulonecrotic skin lesions, arthritis, thrombophlebitis, and colonic ulcers. Shortly after birth the infant presented with transient orogenital ulcerations and pustular cutaneous lesions. On healing, depressed scars developed which were very similar to those of the mother. The finding of circulating immune complexes in the mother’s serum gives some support to the hypothesis that the infant’s transient illness was caused by transplacental passage of maternal antibodies.

Behçet’s disease is a multisystem disorder characterised by aphthous stomatitis, genital ulcers, uveitis, cutaneous vasculitis, and arthritis. Additional findings may include vascular, neurological, gastrointestinal, pulmonary, and renal manifestations. Its aetiology is unknown, although genetic, viral, and immunological mechanisms have been implicated. Epidemiological studies suggest important geographical differences, and a familial occurrence has been reported.

This report describes Behçet’s disease in a mother and her newborn infant. The infant presented shortly after birth with extensive orogenital ulcerations and pustular cutaneous lesions. The acute lesions resolved spontaneously in 6 weeks, leaving depressed scars over face, tongue, and palate. Cryoglobulins and circulating immune complexes were demonstrated in the mother’s serum at the time of study. Possible pathogenetic implications are discussed.

**Case history**

A 37-year-old woman with Behçet’s disease had aphthous stomatitis and recurrent oropharyngeal ulcers since 1960. She had had recurrent vaginal and vulvar ulcerations since 1969. Beginning in 1971, recurring aceniform pustules and papulonecrotic lesions developed; some were ulcerated and a few were triggered by trauma. Other manifestations included an episode of depression in 1973; attacks of inflammatory arthritis of elbows, knees, and/or ankles since 1974; superficial thrombophlebitis in 1975 and 1978; and 2 diarrhoeal episodes in 1978 and 1979, one of which was associated with rectal bleeding and colonic ulcers demonstrated by colonoscopy. At the time of the study in December 1979 her symptoms included ulcerations of the oropharynx, gums, lips, and genitalia, associated with arthralgia, fever, and ulcerated lesions over back and one finger. Several puckered scars from previous skin lesions were present over the shoulders, back, and thighs (Fig. 1A).

Results of laboratory evaluation included a haemoglobin (Hb) of 12·5 g/dl, white blood cell count (WBC) of \(8·6 \times 10^9/l\) with a normal differential, and ESR (Westergren) of 35 mm/hour. The absolute lymphocytosis count was \(2·479 \times 10^9/l\) with a normal percentage of T cells (E rosette) and B cells (EAC rosette). Leucocyte function tests revealed normal bactericidal and candidacidal activities, and nitroblue tetrazolium (NBT) test. Leucocyte mobility and chemotactic responses, as measured by the skin window technique, were normal. The platelet count...
was $310 \times 10^9/\text{l}$, and the platelet survival time was within normal limits. Platelet satellitism\textsuperscript{12} (rosettes of platelets around granulocytes) was repeatedly demonstrated during exacerbations. A bone marrow examination was normal. Urine analysis, electrolytes, calcium, phosphorus, alkaline phosphatase, blood urea nitrogen, creatinine, SGOT, and lactic dehydrogenase were normal. Protein electrophoresis pattern was normal with a total of 7 g/dl (70 g/l) and albumin 4 g/dl (40 g/l). Quantitative immunoglobulins showed IgG 1250 mg/dl (normal 800–1800 mg/dl), IgA 330 mg/dl (normal 90–450 mg/dl), and IgM 250 mg/dl (normal 60–280 mg/dl) (SI conversion: g/l = mg/dl × 0.01). Rheumatoid factor, antinuclear antibody, anti-DNA antibody, Coombs's test, VDRL, and HBsAg were negative. At the time of study total haemolytic complement (CH50) and the third and fourth components of complement were within normal limits. Trace amounts of cryoglobulins were detected after 4 days at 4°C. The thrice-washed cryoprecipitate was quantitated spectrophotometrically by measuring ultraviolet absorption at 280 nm of acetic-acid-dissolved aliquot of the cryoprecipitate.\textsuperscript{13} It measured
57 µg/ml. Double immunodiffusion analysis in agar with monospecific antisera against IgG, IgM, IgA, Clq, C3, C4, and human serum albumin revealed a mixed polyclonal IgM-IgG cryoglobulin.

Rheumatoid factor activity was demonstrated in the cryoglobulin by the latex fixation test (Hyland). Cryoglobulins were transient on repeat testing. Circulating immune complexes were also detected with a liquid-phase radiolabelled Clq binding assay.\(^{14}\) Quantitation was performed with a standard binding curve constructed with varying concentrations of heat-aggregated human gamma globulin (HAGG). The concentration of immune complex was 0.15 mg/ml equivalent HAGG (normal: less than 0.1 mg/ml equivalent HAGG). (SI conversion: g/l = mg/ml × 1.)

Delayed hypersensitivity skin test battery gave positive responses to candida, streptokinase-streptodornase, histoplasmin, and mumps antigens. Negative responses were obtained to trichophyton, purified protein derivative and control saline. Biopsy of a skin lesion showed oedema, dense perivascular lymphocytic and neutrophilic infiltration associated with necrosis, and ulceration of epidermis. Assorted therapies including corticosteroids, ACTH, azathioprine, methotrexate, levamisole, and colchicine have not altered the course of the disease.

She has 2 children, a normal daughter born in 1962, and the affected son born in 1968 after an uneventful pregnancy. During both pregnancies the mother experienced recurrent oropharyngeal ulcerations as the sole disease manifestation. Shortly after birth the newborn infant son developed fever, severe stomatitis with oropharyngeal ulcers, and several crusted, ulcerated pustular lesions over the face, scalp, penis, and buttocks. Laboratory tests showed Hb 14.0 g/dl, WBC \(32 \times 10^9/l\) with 56% neutrophils, 15% lymphocytes, and 26% monocytes. The platelet count, urine analysis, and serum protein electrophoresis were normal. Cultures of blood, stools, and oral and skins lesions were sterile. Neonatal herpes simplex infection was suspected but was not confirmed. The mucocutaneous lesions resolved within 6 weeks leaving depressed scars over tongue, palate, and cheeks. The child has remained healthy since, and the mucocutaneous lesions did not recur. He was 11 years old at the time of study in December 1979. Several puckered scars were still present over his cheeks (Fig. 1B), tongue, and palate. There were no active lesions and he appeared otherwise normal. Results of laboratory studies were unremarkable.

On HLA antigen testing the mother's haplotypes were AW30, BW40, and A1, BW17. The 2 offspring were HLA-identical for A and B loci with haplotypes AW30, BW40, and A9, B7.

**Discussion**

The clinical features of the mother were characteristic of Behçet's disease in that she had 3 of 4 major criteria, and 3 minor criteria for the diagnosis of the disease.\(^1\)\(^3\)\(^6\)\(^9\) The infant had stomatitis, genital ulcers, and skin lesions, thus fulfilling 3 of the 4 major criteria. Although the relationship of the infant's illness to the mother's disease was not fully appreciated at the time of birth, there is indirect evidence that it was due to congenitally acquired Behçet's disease. The orogenital ulcers and pustular skin lesions were quite characteristic, and other infections, such as neonatal herpes simplex or impetigo, neither of which cause scarring, were excluded. Another diagnostic clue was provided by the striking similarity between the mother's and the son's scars as observed at the time of study 11 years later (Fig. 1A and B).

The possibility that genetic factors are involved in the pathogenesis of Behçet's disease is supported by a number of observations. A familial occurrence has been well documented.\(^1\)\(^2\)\(^4\)\(^-\)\(^11\) An autosomal dominant inheritance with variable expressivity has been suggested.\(^11\) A raised frequency of HLA B5 antigen has been noted in some studies but not in others.\(^6\)\(^7\) In the present study, although the 2 offspring were HLA-identical for A and B loci, only the son developed the disease. Furthermore, the transient nature of the illness makes a direct genetic transmission unlikely. It is more probable that the infant's disease was due to a transplacentally acquired maternal factor. However, no specific infectious agent was identified in the mother or infant.

Alternatively, the transient Behçet's manifestations in the newborn infant could have been due to transplacental passage of maternal antibodies. Several lines of evidence indicate that alterations in humoral immunity are important in the pathogenesis of the disease.\(^3\) Anti-human oral mucous membrane antibodies,\(^14\) demyelinating antibodies,\(^18\) cryoglobulins,\(^20\) and circulating immune complexes\(^21\) have been demonstrated in sera from some patients with Behçet's disease. In the present study, however, autoantibodies or immune complexes were not sought in the mother or the infant at the time of delivery; hence placental transfer of antibodies was not verified. Nonetheless the mother's serum contained immune complexes and traces of cryoglobulins at the time of the study 11 years later. The fact that the infant has remained healthy with no further mucocutaneous lesions since the age of 6 weeks further supports the hypothesis that the transient Behçet's manifestations were caused by antibodies transferred from the mother. A similar mechanism is known to operate in neonatal systemic
The manuscript.
The authors
and
this
report
of
maternal antibodies.
Behqet's
by transplacental factors. It is
mediated
512
Fam,
bations,11
or no
are largely
been
described.
infants
these
purpura,23
and myasthenia
gravis.24 Few if any of
these infants
developed true disease.
The effects of pregnancy on the course of Behçet's
disease are largely unknown.25 Remissions,2 even
exacerbations,11 or no change, as with our patient, have all
been described.
In conclusion, infants born to mothers with
Behçet's disease may develop transient mucocutaneous
lesions in the newborn period, presumably
mediated by transplacental factors. It is hoped that
this report will stimulate closer observation of these
infants and a chance to verify transplacental passage
of maternal antibodies.

The authors acknowledge the assistance of Drs Judy Falk
and Michel Klein and thank Mrs Janet Hays for preparing the
manuscript.

References

1 Mason R M, Barnes C G. Behçet's syndrome with
2 Chajek T, Fainaru M. Behçet's disease. Report of 41
cases and a review of the literature. Medicine 1975; 54:
179–96.
3 Shimizu T, Ehrlich G E, Inaba G, Hayashi K. Behçet's
disease (Behçet syndrome). Semin Arthritis Rheum 1979;
8: 223–60.
4 Sezer N. Further investigations on the virus of Behçet's
5 Fenech F F, Soler N G. Behçet's syndrome with
II: 475.
6 Berlin C. Behçet's disease as multiple symptom complex:
7 Fadli M E, Youssef M. Neuro-Behçet's syndrome in the
8 Goolamali S K, Comash J S, Hassanyeh F, Stephens A.
Familial Behçet's syndrome. Br J Dermatol 1976; 95:
637–42.
9 Abdel-Aziz A M, Fairburn E A. Familial Behçet's
1978; ii: 1786.
11 Berman L, Trapper B, Jenkins T. Behçet's syndrome: a
family study and the elucidation of a genetic role. Ann
12 Prchal J T, Blakely J. Granulocyte platelet rosettes.
13 Brouet J C, Clauvel J P, Danon F, Klein M, Seligmann M.
Biologic and clinical significance of cryoglobulins, a
14 Nydegger U E, Lambert P H, Gerber H, Miescher P A.
Circulating immune complexes in the serum in systemic
lupus erythematosus and in carriers of hepatitis B
antigen, quantitation by binding to radiolabeled C1q.
16 Ohno S, Nakayama E, Suguiru S, Itakura K, Aoki K,
Aizawa M. Specific histocompatibility antigens associated
17 Ersoy F, Berkel A I, Firat T, Kazakoglu H. HLA
antigens associated with Behçet's disease. In: HLA and
19 Inaba G, Aoyama J, Shimizu T. Clinical and immuno-
chemical studies on neuro-Behçet's syndrome. Clin
20 Scarlett J A, Kistner M L, Yang L C. Behçet's syndrome,
report of a case with pericardial effusion and cryoglobu-
21 Gamble C N, Wiesner K B, Shapiro R F, Boyer W W. The
immune complex pathogenesis of glomerulonephritis
22 Jackson R. Discoid lupus in a newborn infant of a mother
24 Keesey J, Linstrom J, Cokely H. Anti-acetylcholine
receptor antibody in neonatal myasthenia gravis. N Engl
Rodriguez G E. Behçet's syndrome associated with
pregnancy. Obstet Gynecol 1979; 53: (3 suppl): 31s–33s