CLINICAL STUDIES ON BEHÇET'S SYNDROME

BY

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Since Behçet (1937) reported cases with the symptoms of skin eruption, ulceration of the mucous membranes, and hypopyon-uveitis, similar cases have been described by many authors (summarized by Robinson and McCrum, 1950) as the "mucocutaneous ocular syndrome". Cases of Behçet's syndrome have recently been reviewed and reported in Japan by Asaoka (1959) and Urayama (1960). Pathogenetic theories include those of pararheumatic disease (Shikano, 1960), bacterial allergy (Urayama, 1960), and viral infection (Behçet, 1937; Sezer, 1953, 1956; Evans, Pallis, and Spillane, 1957), but none has been widely accepted or confirmed. Moreover, little is known about the systemic manifestations of this syndrome.

The clinical and laboratory findings in 85 cases of this condition seen at our clinic between September, 1957, and April, 1961, are reported below.

Clinical Material

The 85 subjects comprised 53 males and 32 females (sex ratio 1.7 to 1.0), in whom the syndrome was either "complete" (36) or "incomplete" (49). The former showed all four lesions (cutaneous, oral, genital, and ocular) and the latter lacked one or two of them.

Findings

Age.—As shown in Fig. 1, Behçet's syndrome may occur at any age, ranging from 6 to 65 years, though it is uncommon in childhood and advanced age; the incidence on both sexes rises to a peak in the third decade of life, the average age of the male patients being 27 years, and that of the females 26 years.

Frequency of Main Symptoms.—According to our observations Behçet's syndrome could manifest itself as a systemic disease instead of affecting only localized areas of the body, such as the skin, oral or genital mucous membrane, and the eyes. Fig. 2 (opposite) shows the frequency of many symptoms in our 85 cases. Oral lesions (aphthous stomatitis) were found in 98 per cent., skin lesions (such as erythema nodosum, pyoderma, and acneiform and pustular
lesions) in 85 per cent., and ocular lesions in 79 per cent. Articular involvement and genital lesions came fourth, each being found in 64 per cent. In the 36 "complete" cases, the period from the onset to the appearance of all the mucocutaneous-ocular symptoms was usually between 1 and 6 years (range one month to 15 years).

The oral manifestations appeared first in 52 per cent., and second in 32 per cent.; the order of appearance of all the symptoms is shown in Fig. 3.

**Other Manifestations and Laboratory Findings.**—Apart from the triad of this syndrome, various other symptoms and signs were observed, and some (articular, gastro-intestinal, and nervous system involvement) are thought to be of diagnostic importance.

**Articular Involvement.**—This occurred in 54 cases (Fig. 2), and included pain, swelling, tenderness, and/or redness of the knees, ankles, elbows, and wrists. In most cases these symptoms subsided spontaneously but re-appeared episodically one after another. The sites of the articular manifestations are shown in Fig. 4; the small joints were rarely affected, thus differing from the localization of the articular lesions in rheumatoid arthritis. The radiological appearances were almost unchanged.
Gastro-intestinal Involvement.—This appeared frequently. Fifty patients had diarrhoea, abdominal pain, abdominal distension and tenderness, nausea, belching, and loss of appetite. There were 49 attacks during which diarrhoea was observed in 28 per cent., abdominal pain in 28 per cent., abdominal distension in 43 per cent., nausea in 16 per cent., belching in 20 per cent., and loss of appetite in 31 per cent. There were also 42 remissions, during which diarrhoea was observed in 21 per cent., abdominal pain in 14 per cent., abdominal distension in 24 per cent., and nausea in 9 per cent.

141 radiological examinations were carried out in seventy cases (29 "complete" and 41 "incomplete") and these revealed various abnormalities, especially in the small intestine. Fig. 5 shows that abnormalities were more frequently detected during attacks than during remissions, even in the absence of subjective symptoms.

![Graph showing frequency of radiological abnormalities in the small intestine in seventy cases.](image)

The following case histories are typical:

**Case 1, a man aged 25 years**, had predominantly gastrointestinal disturbances; two or three times a month he had acute attacks with exacerbation of the oral and ocular symptoms, and the abdominal pains were sometimes very severe. The small intestine showed a marked hypotonia with gas retention (Fig. 6).

![Case 1, showing marked hypotonia of the small intestine with gas retention.](image)

**Case 2, a boy aged 12**, our youngest case, started with arthralgia at the age of 10. His gastro-intestinal symptoms were pain and meteorism, often accompanied by an acute attack. The ileum showed inflammatory involvement with absence of the normal feather-like pattern and a marked hatching with slight gas retention.

**Case 3, a man aged 28**, with a typical complete syndrome, had acute attacks once or twice a week, and often complained of abdominal pain and meteorism, sometimes severe, resembling subileus. Radiography revealed marked gas retention and hypotonia of the ileum (Fig. 7, opposite).

**Case 4, a man aged 56**, had acute attacks once or twice a month, with pain, meteorism, and diarrhoea. The small intestine was hypertonic and the colon showed an absence of normal haustration and narrowing (lead-pipe form) with localized gas retention in the elongated sigmoid, indicative of colitis (Fig. 8, opposite).

Fat absorption was examined by the oral administration of olive oil labelled with I\(^{131}\), the radioactivity of the blood being measured with a scintillation counter. Fig. 9 (opposite) shows that the blood concentration of I\(^{131}\) was markedly decreased in patients with Behçet's syndrome compared with that in normal control subjects.
BEHÇET'S SYNDROME

Fig. 7.—Case 3, showing marked gas retention with hypotonia of the intestine.

Fig. 8.—Case 4, showing absence of normal haustration and narrowing of the colon, which suggests colitis.

Fig. 9.—Relationship between x-ray findings in the small intestine and $^{131}$I-labelled olive oil absorption ratio (mean values).

This tendency was predominant in patients with radiological enteric signs, the decrease in absorption being more marked during the acute phases than during remissions (Fig. 10, overleaf).

Nervous System Involvement.—Paralysis, severe headache, mental confusion, etc., were observed in four of our 85 cases, and a further 21 cases had lesser symptoms, such as attacks of headache, tremor, or paraesthesia.

Table I (overleaf) shows the cerebrospinal fluid findings in 21 cases examined. Pleocytosis and other abnormalities in the cerebrospinal fluid were not infrequently seen (in 12 of the 21 cases), even in cases with no nervous symptoms.

The two following cases are typical:

Case 5, a woman aged 31 (A in Table I), had complained of recurrent painful ulceration in the mouth for 2 years. One year previously she had suddenly developed blindness in both eyes, attributed by an ophthalmologist to uveitis with retinal haemorrhage, and had been admitted to hospital with a diagnosis of Behçet's syndrome. These disturbances recurred after 2 to 3 months, and 5 months...
later ulceration of the vulva appeared, which subsided within a month.

One month before re-admission she had insidious loss of voluntary control of the right hand, which improved within a few days, and 2 weeks later severe headache began. 6 days before re-admission she fell into a coma, followed by right-sided hemiplegia and impairment of speech.

**Laboratory Findings.**—Haemoglobin 85 per cent., white blood cell count 8,200 with a normal differential count, erythrocyte sedimentation rate 49 mm. in one hour. Tuberculin reaction (1:2,000) negative. Wassermann reaction negative. On lumbar puncture the cerebrospinal fluid pressure was 150 mm. H₂O, with cells 251 per c.mm. (mainly mononuclear), protein 100 mg./100 ml., sugar 43 mg./100 ml. Tryptophane test positive. Culture for tubercle bacilli negative. The serum protein was 8.3 g./100 ml., albumin/globulin ratio 1.15, serum mucoprotein 159 mg./100 ml., and serum glycoprotein 153 mg./100 ml.

**Result.**—The patient's progress on dexamethasone and prednisolone was impressive. The signs of uveitis regressed rapidly and the hemiplegia improved progressively. She was discharged on the 78th day after re-admission.

**Case 6, a woman aged 33** (M in Table 1), had recurrent ulceration of the mouth once or twice a month for 10 years. From March, 1956, she had complained of tender erythematous nodules. One year later her eyes became painful with blurring of vision, attributed by an ophthalmologist to retinal haemorrhage, which subsided gradually on treatment with cortisone.

On October 29, 1960, she was admitted to hospital with severe headache, fever (101°F.), and confusion. Ophthalmoscopic examination revealed bilateral retinitis proliferans and retino-choroidal atrophy.

**Laboratory Findings.**—Haemoglobin 109 per cent., white blood cells 6,600 with relative neutrophilia, erythrocyte sedimentation rate 21 mm. in one hour. Tuberculin reaction positive. Lumbar puncture revealed opalescent, non-xanthochromic cerebrospinal fluid under an initial pressure of 210 mm. H₂O and a final pressure of 75 mm. after withdrawal of 10 ml. fluid. The fluid gave a ++ Pandy test with 347 cells per c.mm. (mainly lymphocytes), sugar 70 mg./100 ml., chloride 128 mEq./l.
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**TABLE 1**

NERVOUS SYMPTOMS AND CEREBROSPINAL FLUID FINDINGS IN 21 CASES

<table>
<thead>
<tr>
<th>Case Ref.</th>
<th>Sex</th>
<th>Nervous Signs or Symptoms</th>
<th>Pressure (mm. H2O)</th>
<th>Cells (per c.mm.)</th>
<th>Protein (mg./100 ml.)</th>
<th>Nonne-Apel Test</th>
<th>Sugar (mg./100 ml.)</th>
<th>Chloride (mEq./l.)</th>
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<tr>
<td>A</td>
<td>F</td>
<td>Severe headache Hemiplegia</td>
<td>150</td>
<td>251</td>
<td>100</td>
<td>±</td>
<td>43</td>
<td>125</td>
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<tr>
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<td>F</td>
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<td>110</td>
<td>36</td>
<td>39</td>
<td>±</td>
<td>44</td>
<td>121</td>
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<tr>
<td>C</td>
<td>M</td>
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<td>20</td>
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<td>±</td>
<td>-</td>
<td>-</td>
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<tr>
<td>D</td>
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<td>39</td>
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<td>54</td>
<td>132</td>
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<tr>
<td>E</td>
<td>M</td>
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<td>123</td>
<td>56</td>
<td>-</td>
<td>-</td>
<td>56</td>
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<tr>
<td>F</td>
<td>M</td>
<td>Paraesthesiae legs</td>
<td>240</td>
<td>40</td>
<td>26</td>
<td>+</td>
<td>70</td>
<td>134</td>
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<td>4</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
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<tr>
<td>S</td>
<td>F</td>
<td>None</td>
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<td>4</td>
<td>-</td>
<td>±</td>
<td>30</td>
<td>-</td>
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<tr>
<td>T</td>
<td>M</td>
<td>Finger tremor</td>
<td>130</td>
<td>5</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>U</td>
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<td>None</td>
<td>160</td>
<td>4</td>
<td>-</td>
<td>±</td>
<td>60</td>
<td>124</td>
</tr>
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</table>

Wassermann reaction negative. Culture for tubercle bacilli negative. Serum protein 6.3 g./100 ml., albumin/globulin ratio 0.9.

At first tuberculous meningitis was suspected, but as anti-tuberculous chemotherapy proved ineffective, a probable diagnosis of Behçet's syndrome was preferred. The patient improved gradually on treatment with dexamethasone and was discharged on September 2, 1961.

**Vascular Involvement.**—Vascular changes sometimes appeared in this syndrome, and two cases with aneurysm were observed.

Case 7, a woman aged 36, had a painful pulsating swelling on her right forearm, which proved at operation to be due to an aneurysm of the ulnar artery. The Wassermann reaction was negative. Microscopically the small arteries near the aneurysm showed obstruction of the lumen with fibrous tissue, swelling of the lamina elastica interna, splitting of the elastic fibres of the media, and slight perivascular cell infiltration (Fig. 11, overleaf).

Cardiac Involvement.—An incomplete right bundle branch block was observed in one case.

Renal Involvement.—Four cases examined showed no renal dysfunction and their biopsy specimens revealed no pathological changes. Very slight proteinuria or microhaematuria was observed in thirteen of 65 cases examined.

Pulmonary Involvement.—None was observed in our cases.

Liver Involvement.—Liver symptoms were not observed, but in three of seventeen cases a slight impairment of liver function was noted by the bromsulphalein test.

Serological Test for Syphilis.—The Wassermann reaction proved positive in three of 23 cases examined.
Serum Protein.—Dysproteinaemia was observed in 77 per cent. of cases. The $x_1^-$, $x_2^-$, and $\gamma$-globulin levels were raised, but the latter was sometimes below normal. The mean serum $\gamma$-globulin values, whether elevated or reduced, were slightly lower a few days after the appearance of oral ulcers than during remission (Fig. 12, opposite). There were some cases in which a T-fraction (between $\beta$- and $\gamma$-globulins) was observed before an acute attack.

Serum mucoprotein levels were above 80 mg./100 ml. in 89 per cent. of cases; this was thought to be important for diagnosis, especially in those with scanty symptoms. These levels were slightly higher during an attack than in remission (Fig. 12).

Serum protein-bound hexose levels were also raised. Their distribution in the albumin and globulin fractions showed a characteristic pattern, i.e. hexoses in the $\beta$-globulin fraction were higher than in the $x_2^-$-globulin, which was often highest in cases with increased mucoproteins. This increase in $\beta$-globulin-bound hexoses was more marked in cases of the complete syndrome than in the incomplete cases, though there was no significant difference between the total protein-bound hexose levels in the two types.

Other Laboratory Findings.—Serum glycoprotein was raised above 130 mg./100 ml. in nearly 70 per cent. of cases examined. The erythrocyte sedimentation rate was raised in 60 per cent. C-reactive protein was positive in 45 per cent. Hypercholesterolaemia was noted in 25 per cent., leucocytosis in 55 per cent., and eosinophilia in 12 per cent.

Circulating Auto-antibodies.—These were investigated against saline extracted human tissues by the tanned-cell haemagglutination test of Boyden (1951). Auto-antibody against oral mucous membrane was proved to be positive in seventeen of forty cases, in four of twenty-five patients with other diseases, and in none of eighteen healthy controls (Table II, opposite). Twelve of the seventeen positive cases had persistent oral lesions.

Auto-antibody against oral mucous membrane was negative in most cases in remission; its titre became higher before an attack and then fell rapidly. However, if the lesions continued for a long time, the titre in some cases remained high (Fig. 13, opposite).

Discussion

Following the first description given by Behçet (1937), reports of this syndrome have accumulated, but they deal mainly with the more striking mani-
BEHÇET'S SYNDROME

**MUCOPROTEIN**

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**γ-GLOBULIN**

---

- - - with oral lesion.  
- - - with oral and ocular lesions.  
R - in remission.

Fig. 12.—Changes in serum mucoprotein and serum γ-globulin before and after onset of oral and ocular lesions.

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**TABLE II**

AUTO-ANTIBODY AGAINST ORAL MUCOUS MEMBRANE

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Cases</th>
<th></th>
<th></th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behçet's syndrome</td>
<td>17</td>
<td>23</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>Aphthous stomatitis</td>
<td>1</td>
<td>5</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>2</td>
<td>12</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Periarthritis nodosa</td>
<td>1</td>
<td>0</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Endocarditis</td>
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<td>Sub-acute thyroiditis</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>0</td>
<td>18</td>
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<td>18</td>
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</table>

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Our attention was drawn to the systemic aspects of the disease, and our investigations have revealed a high incidence of abnormalities of the intestine, cerebrospinal fluid, and plasma proteins. These suggest that this disease affects not only the skin, mucous membrane, and eyes, but other organs as well. It should be emphasized that the radiological abnormalities of the intestine, pleocytosis and increased protein in cerebrospinal fluid, and dysproteinaemia are sometimes marked, even if subjective complaints are mild or absent.
Radiological abnormalities of the intestine and a decrease in fat absorption were prominent and were more marked during acute exacerbations than during remissions. In an acute attack aphthous stomatitis often appears or is exacerbated before the flare-up of ocular lesions.

Similar lesions of the mucous membranes might be expected to develop in the gastro-intestinal tract, and in one case with gastro-intestinal disturbance a mucosal ulceration of the jejunum with cell infiltration was confirmed by punch biopsy.

Neurological involvement has been described by many authors, and the condition was designated "neuro-Behçet's syndrome" by Cavara and D’Ermo (1955). The various nervous system disorders have been classified by Pallis and Fudge (1956) as a brain stem syndrome, a meningomyelitis syndrome, and an organic confusional syndrome. Abnormalities of the cerebrospinal fluid, such as pleocytosis and increased protein, were demonstrated by Whitty (1958). Cases with neurological involvement are said to have a graver prognosis. Clinical nervous involvement was observed by Asaoka (1958) in five of twenty cases (25 per cent.), and was seen in 25 of our 85 cases (29 per cent.). Changes in the cerebrospinal fluid were observed more frequently, being found in twelve of 21 patients (57 per cent.) who showed few neurological symptoms or none.

Cardiac, pulmonary, or renal involvement was rare and very slight, but vascular changes were sometimes marked.

Dysproteinæmia was the most distinct abnormality found in the course of our laboratory investigations and seemed to be important diagnostically. A raised serum mucoprotein level was observed in 89 per cent., and remained high even in remission. Among the changes in serum protein fractions, decrease in albumin, increase in globulin (especially of the γ-fraction), and lowering of the albumin/globulin ratio were of note, resembling the findings in inflammatory or infectious conditions. It was found that the mucoprotein and γ-globulin levels changed in relation to the onset of acute attacks, the former being inversely proportional to the latter. In 24 cases examined, serum-protein-bound hexoses were sometimes higher in the β-globulin than in the other fractions. This change is considered to be characteristic of this syndrome, because in rheumatoid arthritis and other collagen diseases no such change is observed. It is assumed that these abnormalities of the serum proteins reflect tissue changes in various organs, suggesting a systemic disease.

From this standpoint, the auto-immune mechanisms were investigated. Gajdusek (1958) and others have found complement-binding antibodies against human tissue antigens in lupoid hepatitis, liver cirrhosis, systemic lupus erythematosus, and other collagen diseases.

Bunim (1961) demonstrated circulating antibodies against thyroid and nuclear substance in Sjögren's disease, but the auto-immune mechanism has not yet been investigated in Behçet’s syndrome. Our studies with a tanned-cell haemagglutination test revealed that antibody against human mucous membrane occurred in 42 per cent. of forty cases, and that its titre changed with the appearance of oral symptoms while it proved negative in the healthy controls. Even though the demonstration of circulating antibody against oral mucous membrane does not directly indicate auto-immunization as a primary causative factor, it suggests that an auto-immune mechanism may be involved in the pathogenesis and development of the characteristic clinical picture of Behçet’s syndrome.

Summary

85 cases of Behçet’s syndrome seen in our clinic have been reviewed, and the clinical features and laboratory findings analysed. The clinical manifestations were not localized solely to the regions and systems of the body in which the "triad" appears, but extended to other organs and tissues. A high incidence of involvement of the digestive tract and nervous system and of dysproteinæmia is characteristic of this syndrome, which may be regarded as a systemic disease affecting the visceral organs on a wide scale. The possibility that an auto-immune mechanism may play a role in its pathogenesis is discussed.

Our thanks are due to Prof. E. G. L. Bywaters who kindly reviewed this paper.

REFERENCES


Études cliniques du syndrome de Behçet

RÉSUMÉ

On passe en revue 85 cas de syndrome de Behçet vus dans notre clinique et on en analyse les caractères cliniques et les résultats de laboratoire. Les manifestations cliniques n’étaient pas localisées à ces régions et systèmes du corps où apparaissait la “triade”, mais s’étendaient aussi aux autres organes et tissus. Une grande fréquence de l’implication de la voie digestive et du système nerveux, ainsi que de la dysproteinémie est un trait caractéristique de ce syndrome, qui peut être considéré comme une maladie générale impliquant les viscères sur une grande échelle. On discute le rôle possible d’un mécanisme auto-immune dans sa pathogénie.

Estudios clínicos del síndrome de Behçet

SUMARIO

Se revisan 85 casos de síndrome de Behçet vistos en nuestra clínica y se analizan los rasgos clínicos y los resultados de laboratorio. Las manifestaciones clínicas no se limitaban a las regiones y a los sistemas del cuerpo donde aparecía la “triada”, sino se extendían también a otros órganos y tejidos. Una gran frecuencia de la implicación de las vías digestivas y del sistema nervioso, así como de la disproteinemia es un rasgo característico de este síndrome, que se puede considerar como una enfermedad general implicando los órganos viscerales en gran escala. Se discute la posibilidad de que un mecanismo auto-inmune desempeñe un papel en su patogenia.
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*Ann Rheum Dis* 1963 22: 36-45
doi: 10.1136/ard.22.1.36

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