MONARTICULAR BRUCELLAR ARTHRITIS IN CHILDREN

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Brucellosis is primarily a disease of animals but is often transmitted to man either by drinking raw milk; by direct contact through the broken skin or the conjunctiva; or by the inhalation of infected dust. In Britain almost all infections are caused by Brucella abortus, and in a survey carried out by the Ministry of Agriculture, Fisheries and Food in 1964 it was estimated that between 25,000 and 30,000 herds were infected with an average infection rate of 2-7 cows per herd. The incidence of infection in Scottish herds is thought to be about half of those in England and Wales, but in the North of Scotland it is estimated that about 23 per cent of herds are infected (Munro 1966). In Britain there is no slaughter policy for infected animals, and, while the Milk (Special Designations) Scotland Order of 1965 requires the segregation from a herd of any animal which shows evidence of disease, this requirement is commonly evaded. Even when positive cultures are obtained from an animal the authorities have no power to compel pasteurisation. Since brucellosis in man is not a notifiable disease it is difficult to assess the true incidence, particularly in certain rural communities where only unpasteurised milk may be available to farm workers and those living in villages or small towns. In many parts of Britain it is now a more common cause of joint infection than tuberculosis.

CLINICAL FEATURES

Brucellosis is notoriously a protean disease, but most bacteriämic cases have the classical symptoms of recurrent fever, lassitude and sweating at night. In the localised form of the disease there may be little, if any, constitutional upset and the diagnosis is consequently more difficult.

Monarticular arthritis is one of the localised forms of brucellosis which have received relatively little attention in the literature, although Coventry, Ivins, Nichols and Weed (1949) reported four cases of brucellar coxitis and Makin, Alkalaj and Rozansky (1957) described two further cases, one involving the hip and the other the knee. In the present series of cases not only was a single joint usually involved but all were in children under twelve. Brucellosis is considered to be a rare disease in children, and Wallis (1957) asserted that the incidence in England was 1 per cent of 3,000 children seen over a period of five years. Although it was not possible to estimate the incidence of the disease in children in the north-east of Scotland, as the patients examined were confined to those who were sent to hospital, our experience suggests that local manifestations of brucellar infection are much more common than is generally supposed.

THE PRESENT SERIES

Between 1960 and 1965 eight patients suffering from localised brucellar infection have been treated at the Royal Aberdeen Hospital for Sick Children. Five were girls and three boys, the youngest being one and a half and the eldest eleven. The hip was involved in three children, the knee in two, the ankle in two and the wrist in one. The duration of symptoms was short, varying from a day or two to three weeks. A limp, swelling of the joint and pain were the presenting symptoms, and in the seven cases involving the lower limbs a limp was a constant finding. Of the three children with involvement of the hip only two complained of pain, but all had limited movements with spasm, and Thomas's test and Gauvain's sign were positive. Radiographs were negative, not even showing distension of the joint capsule. Pain was present
in the three children who had knee involvement, but in only two of the cases was swelling noticed by the parents. On examination, however, the striking feature was the degree of synovial thickening with some increase in temperature but only a trace of fluid in the joint. In contrast to tuberculous infection there was much less spasm, but movements were always limited. In one of the patients with knee involvement there was a return of symptoms after discharge from hospital, but, although the patient complained of pain in the foot, clinical examination failed to reveal any abnormality. Radiographs of these three cases merely confirmed soft-tissue swelling.

The boy with a wrist infection complained of pain and swelling. There was some muscle spasm and limitation of movement and the joint was so warm and swollen that the initial diagnosis was septic arthritis.

The two children who had infections of the ankle complained of limp and swelling, with aching pain. In both there was some limitation of movement, but the striking feature was synovial thickening with a doughy swelling obscuring the bony landmarks. One of these children, a twin boy, presented a fairly typical history.

**CASE REPORT**

A boy of two and a half (Case 4 in Tables I and II) was first seen in February 1960. His mother said that he had been slightly "off colour" and had been limping for about two weeks. The right ankle was slightly swollen but there was a good range of painless movement and no local tenderness. Radiographs showed only soft-tissue swelling. The temperature was normal and the erythrocyte sedimentation rate was 5 millimetres in the first hour. Adhesive bandaging was applied from below the knee to the toes. He attended again a week later when his mother said that he was much better in himself and that he was no longer limping. The ankle was still slightly swollen. The bandaging was removed and a crépe bandage applied. Two weeks later the ankle appeared clinically normal and he was discharged.

Three months later he was referred to the orthopaedic clinic with a recurrence of pain and swelling. There was then considerable soft-tissue thickening around the joint, with slight limitation of movement and a little muscle spasm. Radiographs showed soft-tissue thickening and a suggestion of a cystic area in the body of the talus. He was admitted for further investigation and was in hospital for one week. During this time his temperature never exceeded 99 degrees Fahrenheit (37.2 degrees Centigrade) and in view of this a blood culture was not done. Subsequently in one other case in the series a positive blood culture was obtained from a patient with a normal temperature and a normal erythrocyte sedimentation rate.) The haemoglobin was 69 per cent; the erythrocyte sedimentation rate 14 millimetres in the first hour; the total white blood count 7,250 with 27 per cent polymorphs and 63 per cent lymphocytes; the Heaf test, Rose-Waaler and rheumatoid arthritis latex tests were all negative, but agglutination to *Brucella abortus* was positive in a dilution of 1 : 1,280. The Brucellin skin test was carried out later and was found to be markedly positive. He was treated with chlorotetracycline (125 milligrams six hourly); the muscle spasm rapidly disappeared, although the ankle remained swollen. He was allowed home after a week in a below-knee walking plaster, and this was kept on for two months until all swelling had disappeared.

There has been no recurrence of pain or swelling but serial radiographs showed a gradual increase in the size of the cystic area in the body of the talus. This was most marked in a film taken about a year after the onset (Fig. 1). It thereafter gradually decreased in size and finally disappeared. The ankle is now clinically and radiologically normal.
None of the patients in the present series suffered from much constitutional upset and, when examined, their temperatures were not over 100 degrees Fahrenheit (37.8 degrees Centigrade). Three of the children had been "off colour" for a few days and one of them had an attack of diarrhoea five days before admission to hospital. In all cases radiographs of the chest were normal and the Mantoux tests, Rose-Waaler and rheumatoid arthritis latex tests were negative. Antistreptolysin titres and urinalysis gave normal results. The erythrocyte sedimentation rate varied between 3 and 58 millimetres in the first hour but when raised did not appear to be related to the degree of muscle spasm or joint swelling. Haemoglobin estimations were nearly always low, ranging from 63 to 90 per cent and the white cell count was in some cases also low, with a low percentage of neutrophils and an increase in the lymphocyte count (Table I).

**TABLE I**

**CLINICAL AND LABORATORY DETAILS OF EIGHT PATIENTS WITH JOINT LESIONS**

<table>
<thead>
<tr>
<th>Case number</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Joint involved</th>
<th>Duration (weeks)</th>
<th>Erythrocyte sedimentation rate in the first hour (millimetres)</th>
<th>Haemoglobin (per cent)</th>
<th>White blood count (per 1,000)</th>
<th>Lymphocyte</th>
<th>Hospital stay (weeks)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>6½</td>
<td>Hip</td>
<td>2</td>
<td>22</td>
<td>73</td>
<td>2.4</td>
<td>54</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>10½</td>
<td>Knee</td>
<td>3</td>
<td>58</td>
<td>81</td>
<td>8.1</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>2</td>
<td>Hip</td>
<td>1</td>
<td>3</td>
<td>63</td>
<td>9.6</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>2½</td>
<td>Ankle</td>
<td>2</td>
<td>5</td>
<td>69</td>
<td>7.2</td>
<td>63</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>4</td>
<td>Ankle</td>
<td>Under 1</td>
<td>43</td>
<td>77</td>
<td>3.7</td>
<td>35</td>
<td>Out-patient</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>1½</td>
<td>Knee</td>
<td>Under 1</td>
<td>40</td>
<td>80</td>
<td>5.6</td>
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<td>7</td>
<td>Male</td>
<td>3½</td>
<td>Wrist</td>
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<td>8</td>
<td>75</td>
<td>7.4</td>
<td>34</td>
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</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>4½</td>
<td>Hip</td>
<td>Under 1</td>
<td>68</td>
<td>78</td>
<td>4.7</td>
<td>56</td>
<td>7</td>
</tr>
</tbody>
</table>

In all cases the children came from areas where brucellosis is known to be endemic or where there was a likelihood of drinking unpasteurised milk. While there was no history of infection in other members of the families of these children the parents of three had close farming connections and at least two of the children were known to drink milk from herds where there had been premature calving.

**LABORATORY INVESTIGATIONS**

Unequivocal evidence of brucellar infection requires isolation of the causative organism but this is seldom achieved in the localised form of the disease. Only in one of the present series of cases was a positive blood culture obtained and in another child blood culture was negative. Whether positive blood cultures would have been obtained in the other cases may be doubted as there were little or no systemic symptoms. Laboratory diagnosis therefore initially depended on the *Brucella abortus* serum agglutination test which is standard and widely used, but which has several disadvantages. Claims are often made that a particular level of agglutinin (for example 1 : 100 or 1 : 200) is significant of infection, but this may be misleading. Clinically typical disease occasionally occurs with titres under those levels and, on the other hand, titres of this order may be found in apparently healthy individuals in an area where the disease is endemic. When possible, one should demonstrate, during the course of illness, a titre of antibody rising to a level not found among healthy people of the same age group and living in the same area. Appropriate specimens of sera from the present group of
patients were not available to demonstrate rising titres, but we have not found agglutinating antibody levels of the order shown in Table II in the absence of infection, or in a control group of fifteen healthy children from the same areas and of the same age group. Since the clinical features in the present series of cases were those of the supposedly rare localised form of brucellosis it was thought necessary to confirm the laboratory diagnosis by methods other than the standard agglutination test.

Anderson, Jenness, Brumfield and Gough (1964) found that in experimental infection of cattle with *Brucella abortus* strain 19, agglutinins (which developed first) were inactivated by mercaptoethanol, and that the appearance and development of complement-fixing capacity in sera coincided closely with the mercaptoethanol stability of the agglutinins for brucella. Reddin, Anderson, Jenness and Spink (1965) extended these observations to infections in man and claimed that patients with bacteriologically-proved brucellosis consistently have mercaptoethanol resistant IgG (7 S gamma) type agglutinins which differentiate active from inactive infections. IgM (19 S gamma) agglutinins, which are mercaptoethanol sensitive macroglobulins, appear early after infection but persist longer, and are often present in patients lacking clinical or bacteriological evidence of infection. Heremans, Vaerman and Vaerman (1963) found that of the three immunoelectrophoretically distinguishable brucellar agglutinins isolated from human sera, only the IgG fraction fixed complement intensively.

### TABLE II
RESULT OF SEROLOGICAL TESTS IN EIGHT CHILDREN WITH JOINT LESIONS
(Numbers are reciprocals)

<table>
<thead>
<tr>
<th>Case number</th>
<th>Standard agglutination</th>
<th>Mercaptoethanol resistant agglutination</th>
<th>Complement fixation test</th>
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<tbody>
<tr>
<td>1</td>
<td>1,280</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>2</td>
<td>1,280</td>
<td>160</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>1,280</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>1,280</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>5</td>
<td>640</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>6</td>
<td>640</td>
<td>640</td>
<td>Not done</td>
</tr>
<tr>
<td>7</td>
<td>1,280</td>
<td>1,280</td>
<td>160</td>
</tr>
<tr>
<td>8</td>
<td>2,560</td>
<td>1,280</td>
<td>160</td>
</tr>
</tbody>
</table>

In view of these claims and because of the need to obtain as adequate serological evidence as possible, in the present type of case we have tested all available samples simultaneously by a standard agglutination test, by agglutination tests after treating the serum with 0·1 Molar mercaptoethanol and by complement fixation methods. The agglutinating suspension used was a single batch obtained from Burroughs Wellcome and all tests were carried out in 3 × ½ inch tubes, incubated at 50 degrees Centigrade and read after twenty-four hours. In addition to the usual controls, tests were also included with the International Standard serum. Complement fixation tests were carried out using diluted standard suspension of *Brucella abortus* as antigen, and fixation was allowed to proceed overnight at 5 degrees Centigrade. The results of the three tests are shown in Table II.

**DISCUSSION**

Brucellosis is usually considered to be a rare disease in children and until 1938 only a handful of cases was reported in the literature. Since then a few small series of cases have
been described. In 1957 Wallis estimated that the incidence in England was 1 per cent of 3,000 children seen over a period of five years. Many possible explanations have been given for the apparent freedom of children from brucellosis but none is entirely convincing and attention must be given to McCullough’s (1955) suggestion that the disease appears to be rare, as it is seldom considered in the differential diagnosis. The present series of cases would suggest that the incidence of the disease in children may be higher than is usually thought.

The clinical features of brucellosis in adults are notoriously protean and this is equally true of children. In a series of seventeen cases, described by Bothwell (1962), nearly half had fever but three presented with nausea and vomiting, three with listlessness and tiredness and two others with sore throat. Involvement of the joints in adults is well recognised but the type of case we have described in children may readily be missed. Constitutional symptoms were almost entirely absent and the symptoms of limp, swelling and pain in the joints were generally of short duration. The condition appeared to run a benign course and to respond readily to rest and antibiotic therapy. Nevertheless the organisms in brucellosis have a tendency to remain latent in the tissues for prolonged periods and to induce hypersensitivity. We think, therefore, it is important not only to recognise these cases but to follow them up over a long period.

Finally, it is important to comment on the laboratory diagnosis of these atypical cases. Five had a raised erythrocyte sedimentation rate but only three a marked lymphocytosis. While it was not possible to investigate the sera of all cases by the three serological methods used, the findings both on mercaptoethanol treated samples and by complement fixation methods support the results of standard agglutination test. We have found that in adults the former two methods usually run almost parallel but discrepancies occur as in this short series. If the claim of Reddin et al. (1965) that the presence of IgG type of agglutinin denotes active or recent infection is correct, then the tests with mercaptoethanol treated samples of sera in the present series strengthen the diagnostic significance of the high titres found by standard agglutination tests. The significance of any particular agglutinin titre can only be assessed in the light of local epidemiological information and, in routine diagnostic tests as well as in a control series of fifteen children from the same area, we have not found titres of the order listed in Table II in the absence of infection.

From the laboratory point of view, therefore, there is strong evidence that the cases described in this series had recently been infected with \textit{Brucella abortus}. The exact pathology of the lesion in the joints is not known, and whether sensitivity plays a part in the lesion can only be surmised. What is clear is that all of the children had a concurrent brucellar antigenic stimulus which produced antibody in high titres. Moreover in three of the children from whom we have had serial specimens, IgG antibody has declined rapidly and become negative following recovery while IgM antibody has remained raised, although not at the original high titres. This is additional evidence for the causal relationship of the infection to the joint lesions.

While isolation of the causative organism is the only definitive method of diagnosing brucellosis, it may be considered that it would be unlikely to be demonstrated in the localised form of the disease which we have described. However, it is of interest that in one of two children examined by this method a positive blood culture was obtained at a time when the child had a normal temperature and a normal erythrocyte sedimentation rate. When bacteriaemia is present then chemotherapy is obviously necessary but, in the present series, the children seemed to respond to rest alone.

\textbf{SUMMARY}

1. Eight cases of monarticular brucellar arthritis in children are described. They have been followed up from between one and six years and all are now fully active and clinically normal.
2. The history was usually short, with limp, swelling of the joint and pain as the presenting symptoms. Constitutional disturbance was slight in all cases.

3. Diagnosis was confirmed by high concurrent serum agglutinin titres which were not found in control children of the same age from the same areas. Mercaptoethanol resistant antibody (IgG) and complement fixing antibodies were also demonstrated in the sera of four cases. One child had a positive blood culture.

4. The condition responded rapidly to rest and splintage and, to date, recovery seems to have been complete.

We wish to thank Dr A. Gordon Laing, of Tarves, Aberdeenshire, for kindly obtaining sera from healthy children, and Miss Wanda Elmslie for invaluable technical assistance.

REFERENCES


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