BCG OSTEOMYELITIS

EXPERIENCE IN THE STOCKHOLM REGION OVER THE YEARS 1961–1974

S. BERGDAHL, M. FELLÄNDER and B. ROBERTSON, STOCKHOLM, SWEDEN

Eighteen cases of bone and joint tuberculosis in children were diagnosed in the Stockholm region (about 1,500,000 population) over the period 1961–1974. BCG infection was verified by culture and identification of bacterial type in seven, all after 1968. The same origin can be presumed in most of the remaining eleven cases, in spite of the absence of bacterial verification.

The increased frequency of complications after BCG vaccination may necessitate a revision of the vaccination programme.

We recommend operative treatment, which has not led to any growth disturbance or impairment of joint function, although the lesions were invariably localised close to growth zones and joints.

Complications from BCG vaccination are uncommon. The most serious is generalised BCG infection (Thrap-Meyer 1954; Waaler and Oeding 1954; Ustvedt 1956; Horwitz and Meyer 1957); thirteen deaths from this cause were reported by Mande (1968) from the world literature. Bone and joint tuberculosis after BCG vaccination has been described mostly by Scandinavian authors (Mørkbak 1954; Imerslund and Jonsen 1955; Haraldsson 1959; Felländer 1963; Foucard and Hjelmstedt 1971). One of us reported ten cases of tuberculous osteomyelitis in children under five years of age from the decade 1951–60 (Felländer 1963). In one of these cases BCG osteitis was verified by culture and identification of bacterial type; in the others the disease showed similar clinical and radiological features and ran a similar benign course.

In recent years we have observed an increase in the number of cases of BCG-verified osteitis in the Stockholm region. The object of the present study is to throw further light on the clinical and histological aspects of this complication, in the hope of initiating a general revision of the vaccination procedure (Wallgren 1956).

DIAGNOSIS

BCG is a bovine strain of *M tuberculosis* of low virulence. It is not pathogenic to guinea-pigs and not easily differentiated from other bovine strains.

The clinical diagnosis is difficult to establish. The following are suggestive features: a benign course; general condition good; temperature and erythrocyte sedimentation rate moderately elevated. The interval between BCG

vaccination and the onset of symptoms is usually from a few months up to five years.

The radiographic appearance of BCG osteomyelitis is invariably that of a well defined process mostly localised to the epiphyses and metaphyses of the long bones, occasionally extending across the epiphysal line. Radiographically, the condition cannot be distinguished with certainty from chronic non-specific osteomyelitis.

Examination of material removed at operation or biopsy settles the diagnosis. A confident diagnosis requires growth of the BCG strain in culture for the tubercle bacillus and a negative guinea-pig test. The origin might be presumed to be the same in other cases with negative cultures, provided the histological picture is typical of tuberculosis.

CLINICAL MATERIAL

In the fourteen years 1961 to 1974, bone and joint tuberculosis was diagnosed in eighteen children from the Stockholm region, most of whom were treated in the Department of Orthopaedic Surgery, St Görans Sjukhus. Since this is a special department for bone and joint tuberculosis, all cases in the region are likely to have been reported to us.

The diagnostic criteria were positive culture or typical histological findings.

The age at onset of symptoms varied between five months and five years (mean one and a half years). The age at the time of diagnosis ranged from ten months to five years (mean two years). There were equal numbers of girls and boys.

The clinical features were essentially the same as that described above: namely a chronically benign course,

Dr S. Bergdahl, Department of Paediatric Surgery }
Dr Mac Felländer, Orthopaedic Department } St Görans Sjukhus, Box 12500, 112 81 Stockholm, Sweden.
Dr B. Robertson, Department of Pathology }

TABLE I
CASES OF TUBERCULOUS OSTEITIS IN CHILDREN UNDER FIVE YEARS OLD DURING THE PERIOD 1961-1974

Case number	Age (years)	Sex	Interval between onset and operation (months)	Erythrocyte sedimentation rate (millimetres in first hour)	Site of lesion	Histological examination	Bacteriological examination TB culture	Type
1	1 $\frac{8}{12}$	Female	9	Normal	Talus	Tuberculosis	Negative	
2	1 $\frac{8}{12}$	Male	6	35	Proximal epiphysis of tibia	Tuberculosis	Negative	
3	5	Female	3	40	Femoral neck	Tuberculosis	Negative	
4	2 $\frac{8}{12}$	Female	19	29	Proximal epiphysis and metaphysis of tibia	Tuberculosis	Negative	
5	1 $\frac{1}{2}$	Female	1	18	Proximal epiphysis of tibia	Tuberculosis	Negative	
6	2 $\frac{1}{2}$	Male	3	40	Proximal metaphysis of fibula	Tuberculosis	Negative	
7	1 $\frac{1}{2}$	Female	8	18	Cuboid bone	Tuberculosis	Positive	BCG
8	4	Female	2	24	Spine. T.7-9	Tuberculosis	Negative	
9	1 $\frac{5}{12}$	Male	1	41	Femoral neck	Non-specific inflammation	Positive	BCG
10	1 $\frac{5}{12}$	Female	6	35	Proximal epiphysis of tibia	Tuberculosis	Positive	BCG
11	1 $\frac{8}{12}$	Male	1	6	Femoral neck	Tuberculosis	Negative	
12	2 $\frac{8}{12}$	Male	2	30	Proximal metaphysis of fibula	Tuberculosis	Positive	BCG
13	1 $\frac{1}{2}$	Male	3	50	Calcaneus	Tuberculosis	Positive	BCG
14	1 $\frac{1}{2}$	Male	6	60	Elbow joint	Tuberculosis	Negative	
15	1 $\frac{1}{2}$	Male	3 $\frac{1}{2}$	50	Proximal metaphysis of humerus	Tuberculosis	Positive	BCG
16	1 $\frac{3}{12}$	Male	1	37	Distal epiphysis of femur	Tuberculosis	Negative	
17	1 $\frac{1}{2}$	Female	2	35	Proximal metaphysis of tibia	Tuberculosis	Positive	BCG
18	2 $\frac{2}{12}$	Female	3	43	Proximal metaphysis of humerus	Tuberculosis	Negative	

moderate elevation of the temperature and erythrocyte sedimentation rate, and no or moderate restriction of the range of movement at the adjacent joint. In some cases an abscess was found at the time of onset, and in some fistulae had formed after previous biopsies.

The localisation of the disease is shown in Table I. In seventeen of the eighteen cases the lesion was solitary; in the remaining child (Case 14) there were multiple lesions on both sides of the elbow, in the humerus, radius and ulna.

Radiographic features—Characteristically there was a well defined bone lesion, usually with only minor reactive changes in the surrounding tissue—periosteal reaction was seldom found and there was only a small sclerotic zone around the lesion (Figs. 1 to 4). Small sequestra were seen in a few cases.

In one child (Case 8) the lesion involved two adjacent thoracic vertebrae, causing anterior destruction, collapse and gibbus formation—changes that in this region are characteristic of tuberculous spondylitis caused by the human organism, both in adults and in children.

No difference in the clinical or radiological features or in the course of the disease was noted between the BCG-verified and the other cases.

TREATMENT

All the children were treated operatively by curettage, with care not to damage the adjacent epiphyseal lines. Any para-osseous abscess or fistula was explored. The wound was closed by primary suture. Short-term immobilisation in plaster was used if required. Triple-drug chemotherapy was instituted as soon as the diagnosis could be verified, usually after a few days when the results of the histological examination were received. Streptomycin was in most cases given intramuscularly for four to six weeks, and rifampicin and isoniazid were given orally for six months.

RESULTS AND OBSERVATIONS

In the children so treated up to the present, healing has taken place without signs of growth disturbances or impairment of function in adjacent joints. Only in one case (Case 14)—the child with multiple lesions around the elbow joint—has the disease process spread to the adjacent joint. Treatment has not yet been completed in this case, but judged by the course so far, the lesion should heal without impairing joint function.

Bacteriological examination—Cultures for tubercle bacil-

lus were negative in eleven and positive in the remaining seven cases. In all the latter cases the type was identified as the BCG strain (Table I). Guinea-pig tests were negative in all the eighteen cases.

Histological examination—Microscopy of decalcified paraffin sections showed a granulomatous process in seventeen cases. The granulomas consisted of epithelioid

the same as that of proliferative or necrotising tuberculosis caused by tubercle bacilli of human type (Fig. 5).

A non-specific inflammatory process alone was seen in one case (Case 9) in which the material sent for investigation consisted of capsular tissue. Staining for acid-alcohol fast bacilli (Hallberg, Ziehl-Neelsen) was negative in all the cases.

FIG. 1

FIG. 2

FIG. 3

FIG. 4

Case 4. Figure 1—Radiograph before operation. Note the large lesion in the proximal epiphysis and metaphysis of the tibia. Figure 2—Seven months after curettage of the cavity through the central part of the growth plate. Figure 3—Twenty-one months after operation. Figure 4—Three and a half years after operation. Irregularity in the central part of the epiphyseal line, but no disturbance of growth.

FIG. 5

Case 6—Histological section showing characteristic features of BCG osteomyelitis. There is granulomatous inflammation with epithelioid cells and giant cells of Langhans type, as well as caseation necrosis (*left upper*). Numerous plasma cells in the inflammatory infiltrate in *right* part of the field. (Haematoxylin and eosin, $\times 295$.)

cells; giant cells of Langhans type and areas of caseation were also seen in most cases. For the rest, the inflammatory infiltrate consisted mainly of lymphocytes and plasma cells; granulocytic infiltration was present in connection with areas of necrosis. With the exception of the profuse occurrence of plasma cells, the histological picture was

DISCUSSION

In recent years an increased number of cases of BCG osteomyelitis have been diagnosed in Sweden. Whether this is due to a true increase in the incidence or to improvement in diagnosis is uncertain, but a compilation

of the cases presented here together with earlier cases from the same department and region (Felländer 1963), which were all examined according to the same principles, indicates that we are concerned with a true increase in the incidence. Figure 6 shows this combined series of

FIG. 6
Distribution of cases over the period 1951 to 1974.

patients divided into six-year periods. In 1974 five cases of bone and joint tuberculosis were diagnosed, two being BCG-verified. The increase in frequency is equally clear if the calculation is based on the number of cases per vaccination year (Fig. 7). The lower frequency in 1973 is probably apparent rather than real because some lesions had not yet become manifest.

The type of BCG strain was identified in all seven cases in which culture for the tubercle bacillus was positive. A noteworthy fact is that in one of these the histological examination of material removed at operation

FIG. 7
Distribution according to year of vaccination.

showed no evidence of a tuberculous process. However, the explanation of this would probably be that only capsular tissue was sent for microscopic examination. In the rest of the cases, in which material from the destroyed bone area itself was examined, there was a distinct granulomatous and usually also a necrotising inflammatory process. Although a positive culture is a criterion for certain diagnosis, it can be presumed—considering the difficulty of cultivating the BCG and in view of the identical clinical and radiographic picture—that BCG vaccination was the cause in at least seventeen of the cases reported here. The only exception is Case 18, in which the radiographic appearance and the gross findings

at operation rather suggested tuberculosis caused by the human type; in this patient the plasmocellular reaction was also much less marked than in the others.

In Sweden virtually all newborn children are vaccinated with BCG in the first few weeks of life in the maternity hospitals. Foucard and Hjelmstedt (1971) found in the literature thirteen cases of BCG osteitis verified by culture, nine of which were reported from Scandinavia. By questionnaires sent to all orthopaedic clinics in Sweden they also found that in the period 1950 to 1970 four cases of culture-verified and twenty-three cases of probable BCG osteitis were known, which would mean a frequency of about 1 in 80,000 vaccinated children. In the Stockholm region an average of 22,000 children were born in each of the years under study, and the mean annual frequency of tuberculous osteomyelitis in the period 1961 to 1974 was 1 in 17,000. The frequency is rising, however; it was no less than 1 in 5,500 for the children born and vaccinated in 1972 (four cases).

The frequency of positive cultures is high in our series, namely seven out of eighteen, all after 1968. In the earlier series from the same clinic and region in the years 1951 to 1960 the frequency of positive cultures was one in ten.

The cause of this increase in the frequency of tuberculous osteomyelitis in children might be a change of the immunological situation (Falkmer, Lind and Ploman 1955; Kaiserling, Lennert, Nitsch and Drescher 1972; Šićević 1972) or a change of the vaccine. Immunophoresis was carried out in nine of the cases reported here (two being BCG-verified) and showed no abnormality. Nor did the clinical picture indicate immunopathy; apart from the disease concerned, all the children were in good health and responded favourably to operation. As regards the vaccine and the vaccination procedure, an investigation by the Swedish Drug Reaction Committee is in progress (Strandberg 1974).

In the present as in the previously reported cases the disease was localised to the metaphyses and the epiphyses of the long bones or to the short spongy bones; this might be associated with the presence of end-arteries in these regions. A noteworthy feature is the rare occurrence of multiple lesions, in spite of a generalised spread of bacteria after vaccination (Gormsen 1956). In the present and the previously reported series multiple lesions were found in three out of the total of twenty-eight patients.

In spite of the favourable prognosis, this disease is not without consequence to the patient. All the children were treated in hospital for several months, many of them undergoing repeated operations before the proper diagnosis was established. Many of the children were initially subjected to lengthy medical investigations.

The only patient in this series (Case 14) in whom there is cause to fear permanent disability is a child who was treated for six months by repeated incisions of abscesses and with penicillin before the proper diagnosis was established. We think that all bone lesions running

a chronic course should be evacuated operatively so as to obtain material for adequate examination.

CONCLUSIONS

Osteomyelitis running a fairly benign course in children of pre-school age should arouse the suspicion of a tuberculous origin, particularly if the disease does not respond

favourably to treatment with usual antibiotics. It is important that an exact aetiological diagnosis be established as early as possible so that adequate chemotherapy can be instituted. Operative treatment is recommended for two reasons: 1) material will be obtained for settling the diagnosis by histological examination and bacterial culture, including identification of type; and 2) the healing process will be quicker.

REFERENCES

- Erikson, U., and Hjelmstedt, Å. (1971) Roentgenologic aspects of BCG-osteomyelitis. *Radiology*, **101**, 575-578.
- Falkmer, S., Lind, A., and Ploman, L. (1955) Fatal tuberculosis from BCG vaccination. *Acta paediatrica*, **44**, 219-236.
- Felländer, M. (1963) Tuberculous osteitis following B.C.G. vaccination. *Acta orthopaedica Scandinavica*, **33**, 116-126.
- Foucard, T., and Hjelmstedt, Å. (1971) BCG-osteomyelitis and -osteoarthritis as a complication following BCG-vaccination. *Acta orthopaedica Scandinavica*, **42**, 142-151.
- Gormsen, H. (1956) On the occurrence of epitheloid cell granulomas in the organs of BCG-vaccinated human beings. *Acta pathologica et microbiologica Scandinavica*, Suppl. 111, 117-118.
- Haraldsson, S. (1959) Osteitis tuberculosa fistulosa following vaccination with B.C.G. strain. *Acta orthopaedica Scandinavica*, **29**, 121-133.
- Horwitz, O., and Meyer, J. (1957) The safety record of BCG vaccination and untoward reactions observed after vaccination. *Fortschritte der Tuberkuloseforschung (Advances in Tuberculosis Research)*, **8**, 245-371.
- Imerslund, O., and Jonsen, T. (1955) Lupus vulgaris and multiple bone lesions caused by BCG. *Acta tuberculosea Scandinavica*, **30**, 116-123.
- Kaiserling, E., Lennert, K., Nitsch, K., and Drescher, J. (1972) Ultrastruktur und Pathogenese der BCG-Histiocytose (sog. BCG-Granulomatose). *Virchows Archiv A*, **355**, 333-353.
- Mande, R. (1968) *BCG-vaccination*. London: Dawsons of Pall Mall.
- Mørkbak, A. (1954) Osteomyelitis ulnae efter B.C.G.-vaccination. *Nordisk Medicin*, **52**, 1482-1483.
- Šićević, S. (1972) Generalised BCG tuberculosis with fatal course in two sisters. *Acta paediatrica Scandinavica*, **61**, 178-184.
- Strandberg, J. (1974) *Personal communication*.
- Thrap-Meyer, H. (1954) Generalized BCG infection in man. I. Clinical report. *Acta tuberculosea Scandinavica*, **29**, 173-179.
- Ustvedt, H. J. (1956) Usual and unusual reactions to BCG inoculation in children. *American Review of Tuberculosis and Pulmonary Diseases*, **74**, Supplement 32-42.
- Waalder, E., and Oeding, P. (1954) Generalized BCG infection in man. III. Autopsy findings. *Acta tuberculosea Scandinavica*, **29**, 188-192.
- Wallgren, A. (1956) Är massvaccination med BCG alltjämt befogad i Norden? *Nordisk Medicin*, **55**, 21-26.