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Osteitis Caused by BCG Vaccination

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Summary: A survey of 26 Czechoslovakian children diagnosed with BCG osteitis during 1981–1986 is presented. Mycobacterial culture was attempted in 19 cases with confirmation of bacillus Calmette-Guerin (BCG) *Mycobacterium bovis* strain in nine cases. Symptoms appeared ~17 months after vaccination; the proximal tibial end, distal femur, and proximal humerus were most affected. Although vaccination has been obligatory since 1953, a different vaccine was introduced in 1980, which led to the diagnosis of BCG osteitis in 1981. The vaccination doses, symptomatology, and methods of treatment are described. The risk of complications and a project for vaccination at later age are discussed. **Key Words:** BCG osteitis—BCG osteomyelitis—BCG osteoartritis—Vaccination of newborns.

Osteitis caused by vaccination of newborns is well known in Scandinavia where bacillus Calmette-Guerin (BCG) vaccination has been performed for decades (2,6,9). Both the liquid vaccine (strain BCG 725 derived from the Copenhagen strain in 1947) and the freeze-dried vaccine from the Japanese strain 172 were prepared in the Institute of Hygiene and Epidemiology (IHE) in Prague and used until 1980 (4). In 1980, the freeze-dried vaccine prepared from strain BCG 1 imported from the USSR was introduced. Soon after its introduction, it appeared that its higher rest virulence was causing complications, especially in newborns (3). In 1981, the first BCG osteitis was diagnosed in Czechoslovakia.

METHODS

In CSR, where BCG osteitis has been followed, ~130,000 newborns (99%) are BCG vaccinated each year, since the BCG vaccination became obligatory in 1953. The vaccination is performed in the maternity wards intracutaneously into the left shoulder on the third to fifth day after birth, provided there is no contraindication (low birth weight, icterus neonatorum, etc.). From 1980 to 1985, one vaccination dose of 0.1 ml contained 0.04 mg, or about one million, viable bacteria. In 1985, this dose was decreased by one-half. For tuberculin testing, the Mantoux test was used, injecting 0.1 ml/2 TU of standard PPD (i.e., batch RT 23 with Tween 80 produced in the State Serum Institute in Copenhagen). Induration of ≥6 mm diameter was classified as positive reaction. The diagnosis was verified by a positive culture, or it was held probable that a BCG infection had occurred when Foucard's criteria were fulfilled (2,13): (a) A BCG vaccination had been performed; (b) <4 years had passed between the vaccination and the onset of symptoms; (c) a known tuberculous contact was lacking; (d) the clinical picture was in agreement with the picture as published in literature dealing with cases of BCG osteomyelitis or osteoarthritis; and (e) in examined cases, the histologic findings indicated tuberculosis. Demonstration and identification of the BCG strain was performed in the IHE in Prague.

RESULTS

The first case of BCG osteitis was diagnosed in 1981 at the Orthopaedic Clinic, Paediatric Faculty of Charles University in Prague. In a patient with chronic gonitis, the *Mycobacterium bovis* BCG strain was isolated and later identified at the IHE in Prague (7,11).

From 1981 to 1986, 26 patients in CSR were diagnosed with BCG osteitis. Twenty-four of these children were vaccinated as newborns and two children were revaccinated at 18 months. At the same time, six cases were diagnosed in the Slovak Republic (eastern part of Czechoslovakia); they are not included in this group. In our group, there are 18 boys and nine girls. Twenty-two cases were verified

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histologically. Mycobacterial culture was performed in 19 patients, and the BCG strain was identified in nine patients. In our group there were three patients with BCG spondylitis, of which two were not verified histologically or bacteriologically. The group is summarized in Table 1. In 50% of the cultivations performed, the BCG strains were identified. On the average, the first symptoms appeared after 17 months (from 11 to 30 months).

Clinical findings

In the affected joints and the long bones, the first symptoms were a change in the child's activity and a swollen joint almost without a hydrops. The joint was warmer, its movements were limited, and contracture beginning to develop. Children with affected spine were tearful and refused to stand up or sit down. Some patients had low-grade fever during the first week. After some weeks, there was pain in the spinal processes where the spine was affected, and an antalgic thoracic block and a lumbal block developed. The suspicion as regards BCG osteitis was supported by the increased erythrocyte sedimentation rate (ESR) value (in our group, the average was 20–30 pH), lymphocytosis, increased inflammatory reactants, and positive Mantoux test (induration from 6 to 35 mm). However, in single cases, reaction was negative. Some patients were also examined immunologically; neither a humoral, nor a cell immunity disturbance was found.

The radiographic picture was typical: in the first phase, osteopenia was evident at the ends of the long bones. Later lacunar foci or a big cavity in the metaphysis reaching the epiphysis appeared. A mild periostal reaction was observed. Multiple cystic foci occurred only rarely. On the vertebrae first osteopenia appears, but gradually lytic foci and compression in the vertebrae develop. In one patient, we saw the shadow of a paravertebral abscess (Fig. 1).

FIG. 1. Tomogram of thoracic spine in anteroposterior projection shows the shadow of a paravertebral abscess and a compression of vertebrae bodies Th 3 and Th 4 3 months after onset of first symptoms; incubation time 11 months.

For diagnostic and therapeutic reasons, a costotransversotomy from Th 4 to Th 6 was performed (Fig. 2). Figure 3 shows the thoracic spine in lateral projection 3 years after the beginning of the illness. The vertebrae bodies are fused; the conic form of

TABLE 1. *Characteristics of group of 26 patients with BCG osteitis*

Site	n	Sex		Incubation (mo)		Culture *Mycobacterium bovis* BCG			Histology	
		Boys	Girls	From–until	Average	Positive	Negative	Not performed	Confirmed	Not performed
Proximal tibial end	6	6		12–30	21.0	2	2	2	6	
Distal femur	5	3	2	11–19	15.4	3	1	1	4	1
Proximal humerus	3	2	1	12–25	17.6	2		1	3	
Proximal femur	2	2		12–15	13.5		2		2	
Spine	3	1	2	11–26	18.5		1	2	1	2
Synovitis knee-joint	2	1	1	12	12.0		1	1	1	1
Distal humerus	1	1		11	11.0	1			1	
Sternum	1		1	15	15.0		1		1	
Talus	1		1	16	16.0	1			1	
Calcaneus	1	1		16	16.0		1		1	
Fibula	1	1		30	30.0		1		1	
Total	26	18	8	11–30	16.6	9	10	7	22	4

the vertebral body Th 4 causes gibbosity of the spine.

Pathologicoanatomic findings

At operation granulation tissue was found in the bone cavities. In our first diagnosed case, pus and numerous corpora oryziodea were found in the knee joint. Microscopically epithelioid cell granuloma with caseous necrosis and giant cells of Langhans type were found. Acid-fast bacilli were never found in a histologic material. The sites of BCG osteitis are shown in Table 1. In the proximal tibial end, osteitis was proven six times, in the distal femur five times (Fig. 4), in the proximal humerus and in the spine three times, in the proximal femur twice, and in the knee joint BCG synovitis was found in one patient. There was one case only of affected sternum, talus, calcaneus, and fibula. In one patient, the affected area was bifocal: After 2 months, the spina ventosa of the basal phalanx of the fourth right hand finger developed beside the proximal tibial end (Fig. 5).

Course

The course of BCG osteitis is similar to osteoarticular tuberculosis (in European literature called "cyclic course") but is milder and, according to experience, the treatment period is about one-third shorter. During treatment the following complications were observed: arthritis, abscesses (also paravertebral), and fistulae in the operation wounds. No severe disturbances of extremity growth were observed; the overgrowth of the affected lower extremity was a maximum of 1 cm. Motion limitation did not exceed 20°. Spondylitis healed by fusion of the neighboring vertebrae. One patient, however, developed gibbosity (Fig. 3) and mild scoliosis (grade Ia after Cobb).

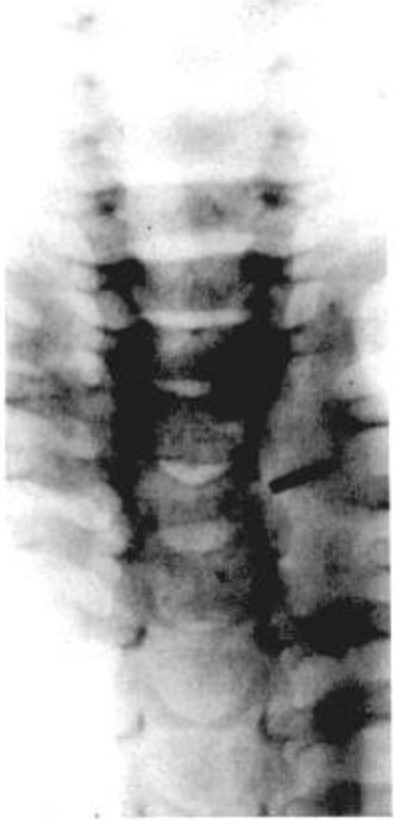

FIG. 2. Anteroposterior radiograph of upper thoracic spine of same patient after left-hand costotransfersectomy from Th 4 to Th 6.

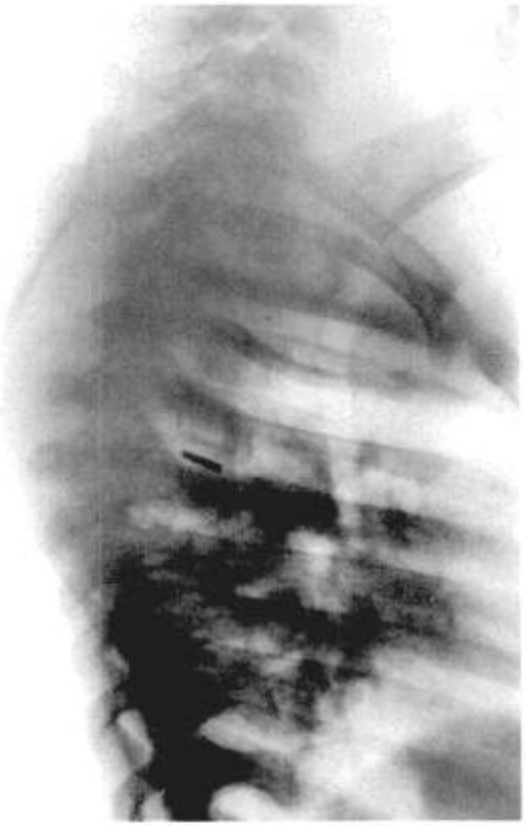

FIG. 3. Radiograph of upper thoracic spine of same patient, lateral projection, 3 years after onset of symptoms shows conic form of Th 4 causing gibbosity.

Treatment

We began treatment of most of our patients by administering antibiotics, since the local symptoms imitate a nonspecific osteomyelitis. Unsatisfactory results suggested tuberculous or BCG etiology. In the first 3 months, the foci were treated surgically (excochleation of the cavern, arthrotomy and lavage, partial synovectomy) and the material thus obtained was examined histologically and bacteriologically. The extremities were immobilized in plaster splints; the patients with spondylitis were immobilized in plaster bed. On verification of the diagnosis, the treatment with antituberculous drugs was started. Best results were obtained when the three-drug regimen of streptomycin (SM), isoniazide (INH), and rifampicin (RMP) was applied in the first 3 months, and then the two-drug regimen of

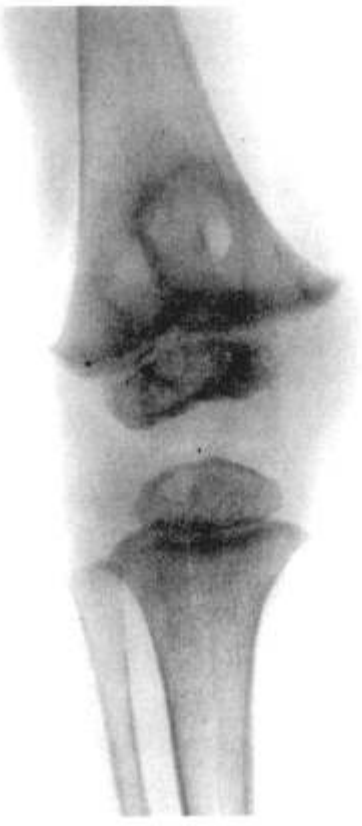

FIG. 4. Radiograph of right knee 2 years after onset of symptoms; incubation period 15 months. Changes in bone structure (postinfectious dysostosis) of both metaphysis and epiphysis of the femur and the proximal epiphysis of the tibia persist.

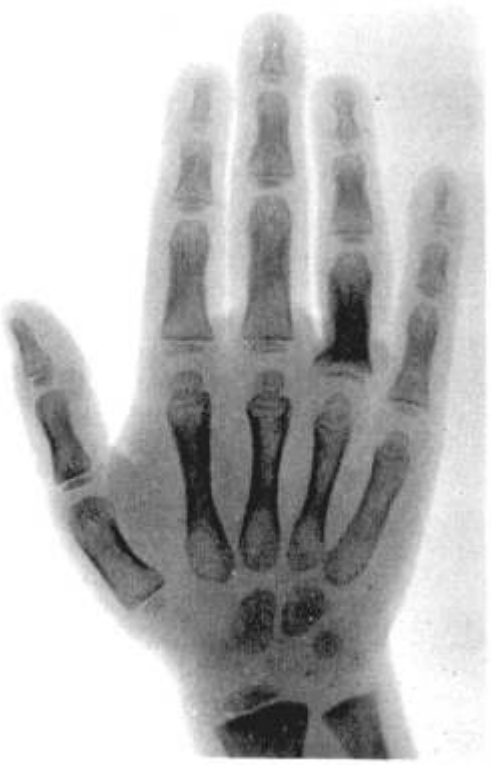

FIG. 5. Radiograph of right hand, anteroposterior projection 2 years after onset of symptoms occurring 30 months after vaccination; bifocal site: BCG osteitis tibiae proximalis 1.dx. and spina ventosa of basal phalanx of fourth finger (bacteriology of fistulae pus confirmed BCG etiology).

INH and RMP was maintained for another 3 months (or even longer); thereafter, only INH was given for ~6 months.

The prolonged therapy of the affected children with BCG osteitis (and osteoarticular tuberculosis) is secured, for the whole Czechoslovak republic, at the Children Institute at Dolný Smokovec in the Tatra mountains. The climate-heliotherapeutic regimen after Rollier takes place in a specialized department of the Institute (height 900 m). An integral part of the therapy is individual rehabilitation and surgical treatment of abscesses with fistulae, which occur particularly in the operation scars.

Differential diagnosis must consider the osteoarticular tuberculosis caused by virulent mycobacteria, nonspecific osteomyelitis, chronic juvenile arthritis, and neoplasms (eosinophilic granuloma, primary malignant tumors, or metastases).

DISCUSSION

The atypical course of BCG osteitis and lack of experience with the affliction, diagnosed in CSR for the first time in 1981 after introduction of the Soviet lyophilized vaccine prepared from the BCG 1 strain, which has a higher rest virulence (4,7), caused some embarrassment, especially with the first cases. We believe that confirmation of *M. bovis* BCG in culture in osteitis is important not only for stating the correct diagnosis but also for the early start of causal therapy.

The problem of BCG osteitis has been dealt with in many scientific papers, above all from Sweden and Finland where this infection occurred most often. About three-fifths of all known cases are reported from these countries. Correlation of the incidence of BCG osteitis in CSR, Finland, and Sweden is shown in Table 2. After 1971 in Finland and after 1972 in Sweden, the incidence of BCG osteitis increased markedly in connection with transfer of BCG vaccine production from Gothenburg to

TABLE 2. *Incidence of BCG osteitis counted per 100,000 newborns*

Strain (Source)	Years used	Incidence	Location
BCG 725 (CSR)	1947–1980	0	CSR
BCG 1 (USSR)	1981–1985	3.6	CSR
Gothenburg	1960–1970	10.0	Finland
(Sweden)	1969–1971	5.0	Sweden
Gothenburg	1971–1977	33.0	Finland
(Denmark)	1972–1975	29.0	Sweden
Glaxo	1978–1982	6.7	Finland

Copenhagen. The variability of incidence shows that various BCG strains, as well as the same strains maintained in different laboratories, may have a varied hematogenic dissemination. Follow-up of strain virulence in animals in Copenhagen in 1970–1975, however, has shown no increase in virulence as compared to the previous time period. According to Lind (5), the cause of the increased number of the postvaccination osteomyelitis cases is unknown.

In Sweden, vaccination of newborns was abandoned in 1975, since 97% of all infections appeared after vaccination at newborn age. In Finland, the vaccination by BCG Glaxo vaccine, imported from England, still continues. Since this vaccine was introduced, the number of BCG cases decreased markedly, but single cases did occur (6). An inborn or acquired disturbance of the immune system certainly also may play a role in development of BCG osteitis. Cases of BCG infections leading to death have been described (2), as has increased sensibility among various ethnic groups. Excessive vaccination doses also play an important part. In Czechoslovakia, the vaccination dose was decreased in 1985 by one-half [0.1 ml = 0.025 mg BCG, ~0.5 million viable bacteria (8)].

The advantage of BCG vaccination and the risk of complications must be considered seriously. For example, Peltola et al. (9) state that in countries where routine BCG vaccination has been stopped (Sweden in 1975, Spain in 1974), cases of tuberculous meningitis in children were reported. In CSR, where the incidence of tuberculosis in children is low (2–3/100,000 in the age group 0–14 years), and meningitis or the miliar form occur only exceptionally, the number of serious BCG complications and the number of serious forms of tuberculosis that can prevented by vaccination, are equal. Therefore, in 1986 in two districts of CSR a new vaccination project was introduced, postponing vaccination of newborns to a later age, when the risk of serious complications is low (12).

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