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BCG-OSTEOMYELITIS AND -OSTEOARTHRITIS AS A COMPLICATION FOLLOWING BCG-VACCINATION

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Severe complications following BCG-vaccination are rare with regard to the great number of vaccinations performed in many countries. BCG-infections leading to death have been reported in 13 cases (Mande 1968). Six of these cases are reported from Scandinavia (Hollström & Hård 1953, Meyer & Jensen 1954, Thrap-Meyer 1954, Falkmer, Lind & Ploman 1955, Gardborg et al. 1963, Carlgren et al. 1965). Clinical data indicate, however, that most of these cases had defective immunity of congenital or acquired type (Matsaniotis & Economou-Mavrou 1966). In some cases there was also a hypogamma-globulinemia.

Of other complications following BCG-vaccination osteomyelitis and osteoarthritis are of special interest. These complications are probably more common than the lethal BCG-infections and seem to occur in persons with apparently normal immunity. We have found 13 reported cases with BCG-etiology, verified by culture. Of these 9 are from Scandinavia and 1 from each of the following countries: Germany, Austria, France, and Algeria (Mimouni 1951, Falkenfleth 1954, Mørkbak 1954, Imerslund & Jensen 1955, Bang, Engback & Nielsen 1960, Haraldsson 1960, Virtanen & Lindgren 1962, Felländer 1963, Sinios et al. 1965, Wallerström & Enell 1966, Dahl & Halvorsen 1967, Sacrez et al. 1967). Similar clinical pictures in BCG-vaccinated children have been reported by several authors (Paisseau, Sorrel & Nguyen Khac Vien 1941, Backman & Wallgren 1954, Felländer 1963), but in these cases cultures had not been performed or had been negative.

Despite the few reported cases of BCG-osteomyelitis or -osteoarthritis, it is possible for any pediatrician and orthopedic surgeon to encounter such cases. Since these cases often give diagnostic difficulties, we have found it of interest to compile the experiences of

cases reported in the literature and of one case of our own with verified BCG-etiology. Moreover, we have tabulated the results of a questionnaire to all pediatric and orthopedic clinics in Sweden concerning possible cases of BCG-osteomyelitis or -arthritis during the last two decades.

MATERIAL

This includes one case of osteomyelitis caused by BCG, verified by culture (case 1), and another 4 cases of osteomyelitis or osteoarthritis (cases 2–5) suspected to be complications of a BCG-vaccination performed in the neonatal period, but in these cases cultures have been negative. All these cases were encountered during a 3-year period.

1. Girl (B-M.A.) born on January 9, 1967. BCG-vaccinated intracutaneously in the neonatal period without abnormal reaction at the injection site. At 15 months of age she sustained slight trauma to her right knee. Afterwards, she was reluctant to stand on the leg and the knee was somewhat swollen. The X-rays were normal 2 weeks after the trauma, but 10 days later an osteomyelitic process was noted with a central breakthrough in the epiphyseal plate. There were intermittent periods of low-grade fever. No reaction could be seen at the vaccination site. Normal amounts of granulocytes, lymphocytes and immunoglobulins were recorded. Micro-sedimentation rate (MSR) 40 mm/hr. Tuberculin positive with Moro test, negative with Mantoux 1/10000 OT. Normal chest X-ray. She was treated with large doses of penicillin, ampicillin, cephalosporin and sulfa. In spite of this treatment there was a progressive destruction, which prompted surgical exploration. The abscess had perforated the cortex and had also spread to the adjacent soft tissues. Culture was negative on material from the marrow cavity, but on material from the periphery of the subcutaneous abscess, growth of acid-fast bacilli was obtained on Loewenstein's medium. Closer examination of this culture at the BCG-laboratory in Gothenburg showed this material to be indistinguishable from a BCG-culture. Guinea pig inoculation caused no reaction. She was treated with INH and PAS for one year. In spite of the breakthrough in the epiphyseal plate the skeletal growth seems to have been grossly normal with a slight tendency to accelerated growth of the femur.

2. (T.J. 661128). A one-year-old boy with osteoarthritis in his left hip and a radiological progress in spite of intensive antibiotic therapy. He had a low-grade fever along with a MSR of 25 mm/hr. Normal immunoelectrophoresis, normal amounts of lymphocytes. Mantoux positive 1/1000. At operation 2 months after the onset of the illness, greyish villous growths were curetted. The histological picture was compatible with tuberculosis.

3. (A.E. 650626). A twenty-month-old boy developed pains, swelling and heat in his left knee. No fever, MSR 20 mm. Neotuberculin test positive. X-rays of his knee, repeated 2 weeks later, showed no skeletal abnormality. The presumptive diagnosis was rheumatoid arthritis and he was treated with acetylsalicylic acid and periodically also steroids with apparent improvement. A new X-ray half a year later

revealed a destruction in the femur metaphysis with a breakthrough to the epiphysis. At exploration, small amounts of sterile pus were found. Histologic examination showed the picture of a chronic granulomatous process.

4. (J.L. 670724). An eighteen-month-old girl who after a slight trauma to the sternum became locally tender and developed an increasing swelling, measuring 3 × 3 cm after 10 days. An X-ray showed destruction of the lower corpus sterni. MSR 26–34 mm, other laboratory data were normal. Radiological examinations of the lungs, skull, extremities and kidneys were normal. The corpus sterni and surrounding soft tissues were extirpated because of suspected malignancy. No culture specimens were taken. Histologic examination showed the picture of tuberculosis.

5. (E-L.E. 680903). A fifteen-month-old girl with increasing pains and swelling in her right ankle after a slight trauma. Two weeks later X-rays showed a destruction of the distal fibular diaphysis, but other bones and the lungs were normal. Histologic examination of excised material showed tuberculosis. No anemia. MSR 15 mm. Normal amounts of immunoglobulins and lymphocytes in the blood. Tuberculin test positive with Mantoux 2 TU PPD. Normal sensitization with dinitrochlorobenzene.

Questionnaire study: Because these 5 cases happened during a 3-year period, the question arose whether an increase in this type of complication following BCG-vaccination had occurred or not. To study the frequency of these complications a questionnaire, concerning verified or suspected cases of BCG-tuberculosis during the period 1950–1970, was sent to all pediatric and orthopedic clinics in Sweden at the beginning of 1970. Ninety percent of the clinics answered with records or record excerpts concerning 28 children. None of these cases had been verified by a positive culture. Therefore, it was only a matter of estimation as to whether a possible BCG-infection had occurred or not. It was held probable that a BCG-infection had occurred when the following criteria were fullfilled:

1. A BCG-vaccination had been performed.
2. Less than 4 years had passed between the vaccination and the moment the child became ill.
3. A known tuberculous contact was lacking.
4. The clinical picture was in agreement with that reported in the literature in cases with BCG-osteomyelitis or -osteoarthritis.
5. In explored cases, the histological picture indicated tuberculosis.

Eight of the cases reported in the questionnaire fullfilled the above criteria. One more child was suspected of having had a BCG-osteomyelitis, but in her case the time interval between vaccination and

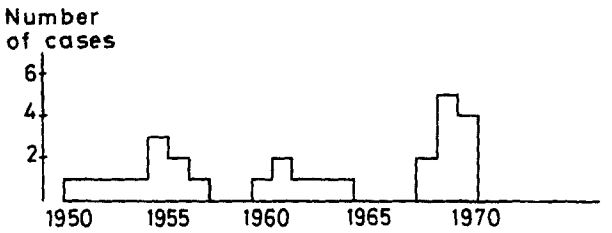

Figure 1. Reported cases of BCG-osteomyelitis or -osteoarthritis from Swedish Departments of Pediatrics and Orthopedics (1950–1970).

apparent disease was 56 months. In spite of that, she was included in the series. In addition to these cases Felländer (1963), Haraldsson (1960) and Wallerström–Enell (1966) have reported one case each of BCG-osteomyelitis verified by growth of BCG. Besides, Felländer reported 9 similar cases where culture had not been taken or had been negative. One more case fullfilling the above-mentioned criteria has been treated in 1961 by one of the authors.

In Sweden, during the period 1950–1970, we now have knowledge of 23 cases of probable BCG-osteomyelitis and 4 cases of BCG-osteomyelitis verified by culture. If the suspected cases really were caused by BCG, the frequency of this type of complication would be about 1:80,000 in BCG-vaccinated children in Sweden. This figure has been calculated from the estimation that more than 90 per cent of all children born in Sweden between 1950 and 1970 (about 2 1/4 million) have been BCG-vaccinated. The distribution in time of the 27 known cases will be seen in Figure 1. It shows a slight increase of the number of cases during the last 3 years, but no definite conclusions may be drawn from the relatively small series.

Clinical, roentgenological, histological and bacteriological findings and treatment results of BCG-osteomyelitis in bones and joints

The following summary is based on the literature data from 13 reported cases of BCG-osteomyelitis or -osteoarthritis and of our own case verified by culture.

Sex distribution: Seven boys, six girls. In one case the sex was not mentioned.

Onset of symptoms: The first symptoms have as a rule been noticed about 12 months after the BCG-vaccination (range 3–26 months).

Clinical symptoms: Usually local swelling, erythema and tenderness. When the process was near a joint there was often a limitation of the

joint movements caused by pain and accompanied by limping when the process was localized to the lower extremities. The general condition was usually normal or only slightly changed. Six patients were said to be afebrile, five had low-grade fever, and for the remaining three information was lacking.

Table 1. Localization of foci in children with BCG-osteomyelitis or -osteoarthritis verified by culture.

Localization of foci	Number of patients	Number of foci
Long bones (epiphyses and metaphyses)	12	13
Ribs	1	6
Vertebrae	2	4
Talus, metatarsus	3	3
Clavicles	1	2
Ilium	1	1
Total	14	29

Localization: In three of the cases there were multiple foci, accounting for a total of 29 foci in 14 patients (Table 1). Twelve of the children had destruction in the metaphyses and/or epiphyses of the long bones. The remaining two children had changes in the talus and the first metatarsal respectively. Foci in vertebrae, ribs, clavicles or the ilium were only found in children who also had a focus in one of the long bones.

Radiological findings: The BCG-osteomyelitis was seen as a localized osteolytic process that could be demarcated and could give the appearance of a cavity. Sometimes a breakthrough in the cortex was noted. In 3 cases there was a cavity both in the distal metaphysis and the epiphyses of the femur with a connecting fistula in the middle of the epiphyseal plate. Reaction in the periosteum in the form of "spina ventosa" was found in one metatarsal bone, and in other cases "thick, stratified periosteal thickening" was noted in the metaphyses of the long bones.

Laboratory data: The MSR varied from normal up to 40 mm/hr. No anemia. The total white counts ranged from 4,800 to 16,800/mm^3 with a normal proportion of lymphocytes. Immunoelectrophoresis was performed in 6 cases; no abnormalities were detected.

The Mantoux reaction: In 9 cases the Mantoux reaction was positive. In another case the reaction was said to be of phlyctenular type. In one case the reaction was negative. In remaining cases information was lacking.

Pathological-anatomical findings: At operation, granulation tissue and small amounts of pus were found. Microscopically epithelioid cell granuloma with central caseous necrosis and giant cells of Langhan's type were seen. In the periphery there were numerous plasma cells and a smaller amount of lymphocytes.

Bacteriological findings: Acid-fast bacilli were found in a smear in one case (Virtanen-Lindgren) and in a histological preparation in another case (Felländer). Culture on Loewenstein's or Loewenstein-Jensen's medium was positive at 37° C in all 14 cases, but was negative at 20–22° and 44–45° where such tests had been performed (Bang et al., Eng & Aaneland, Felländer, Virtanen & Lindgren). At the inoculation on guinea pigs, no or only local infiltration, and sometimes regional lymphadenitis with caseous necrosis, has been observed (Eng & Aaneland, Imerslund & Jensen, Virtanen & Lindgren) but no general dissemination.

Treatment and course: Anamnestic data are very scarce in many cases, but in those cases where information has been given, at least 2 months seemed to have elapsed between the onset of symptoms and the diagnosis. The treatment consisted of local excision or curettage, immobilization, INH, PAS and in a few cases also streptomycin. A primary healing was achieved in most cases, but in some cases a fistula developed. The regression after onset of treatment has been rather rapid. Radiologically the course has ranged from total healing after 6 months to remaining but decreasing skeletal changes after 16 months. In 2 cases a growth disturbance has been reported with a 2 cm shortening of the femur (Virtanen-Lindgren) and a slight shortening of the ulna (Mørkbak). In our own case a slight lengthening of the femur was noted In the case reported by Haraldsson, there was a slight flattening of the trochlea tali.

DISCUSSION

Frequency: The calculated frequency (1:80,000) for BCG-osteomyelitis or -arthritis is probably too low. Incomplete registration and reporting, diagnostic difficulties in tuberculous cases, and possible spontaneous healing before the diagnosis has been settled, might contribute to a

falsely low frequency. Even considering this, the risk of skeletal complications following BCG-vaccination must be regarded as very low.

Diagnostic points of view: It is important to establish an early diagnosis of BCG-osteomyelitis or -arthritis because of the risks of destruction of joints and epiphyseal plates. The diagnosis, however, is difficult to make, which fact is underlined by the period of time, at least 2 months, that usually elapses between onset of symptoms and the tentative diagnosis. The clinical symptoms are uncharacteristic and usually less pronounced, and the blood picture and sedimentation rate show fewer changes compared with other cases of bacterial osteomyelitis in children. BCG-etiology ought to be suspected when the following criteria are fullfilled:

1. The infection seems to be of low virulence.
2. When no regression is seen after some weeks' treatment with antibiotics effective against gram positive cocci.
3. When less than 4 years have elapsed since the BCG-vaccination.

These criteria concern children only. It is uncertain whether these skeletal complications may also occur in BCG-vaccinated adults. When a BCG-osteomyelitis or -arthritis is suspected, the whole skeleton ought to be X-rayed in order to reveal other possible foci. A correct diagnosis can only be obtained with a biopsy and specimens taken for bacteriological and histological examination. The bacteriological specimens ought to be taken both from the pus and the granulation tissue. In most cases there is no growth of acid-fast bacilli in spite of a histological picture clearly indicating tuberculosis. This may probably depend on the low virulence of the BCG. In our tabulation such cases with no growth of BCG were 4 times as common as the cases with growth of BCG (16 of 20 cases). The BCG-etiology may in these cases be suspected but not established.

If culture on Loewenstein's medium shows growth of acid-fast bacilli while the guinea pig test is negative, or only shows local lymphadenitis, there is strong evidence of BCG-infection. To verify the BCG-etiology the suspected colony has to be compared with a BCG colony regarding possible growth when cultured on different media and regarding reaction in sensitivity, inoculation and cytochemical tests.

Treatment: Local excision and/or curettage is a pre-requisite for a correct diagnosis. A complete curettage is desirable along with irrigation and drainage. Immobilization is recommended until clinical heal-

ing is achieved. Antituberculous chemotherapy should be given and as a rule the combination of INH and PAS is enough. Streptomycin may be used exceptionally.

Prognosis: The reported cases have healed rather quickly with treatment. The degree of lasting disability after BCG-arthritis depends on the degree of joint destruction. A growth retardation has been reported in some cases (Mørkbak, Virtanen–Lindgren, Haraldsson) but the disabilities seem to have been of a minor degree.

Etiological points of view: After the BCG-vaccination a dissemination of BCG occurs in the body from the injection site. Within 6 weeks proliferative epithelioid cell groups may be seen in different parenchymatous organs. This dissemination seems to occur whether the vaccine is deposited intracutaneously or subcutaneously. There is a further development of the proliferative changes during the first months, but then they slowly regress (Stojanov & Zagurov 1963). Even 40 months later granuloma rests may be seen in the viscera in some cases (Gormsen 1956). It seems reasonable to suspect these foci to be the origin of the reported skeletal changes. Why there is a progress in these patients is unclear. Examination of isolated BCG-cultures in BCG-osteomyelitis has given no evidence of increased virulence (Bang et al., Wallerström–Enell, Virtanen–Lindgren). Therefore, it is probably the resistance of the vaccinated child that is reduced. Defective humoral immunity with lack of immunoglobulins does not seem to create any obstacle, in contrast to defective cellular immunity, in the development of normal resistance to BCG and human tubercle bacilli (Matsaniotis & Economou–Mavrou, Parkes 1958). However, no humoral or cellular immunity defects have been shown with certainty in the described cases. This may depend on the fact that no defective immunity had ever existed, that our methods for evaluating such defects are too insensitive, or that a defect had existed at the onset of the illness with a normalization at the time of the examination.

Temporarily reduced cellular immunity, manifested by inhibited tuberculin reaction, may be seen in sarcoidosis and such virus diseases as morbilli, varicella, rubeola and influenza. It is possible that certain virus infections may interfere with the response of the host to BCG and this could promote an increased activity in already existing BCG-foci. Imerslund & Jensen have described a local lupus reaction over the BCG-vaccination site in connection with measles 10 months after the BCG-vaccination. Moreover, in one of our own cases of suspected BCG-osteitis, observed earlier by one of the authors, the

onset of the osteomyelitic symptoms was noted a short time after a smallpox vaccination and a local trauma.

It is very difficult to evaluate the importance of a preceeding trauma as a cause of BCG-osteomyelitis, but Rich (1951) finds it probable that such a connection exists. In our questionnaire a preceeding trauma was reported in 13 of the 27 cases.

SUMMARY

1. The authors give an account of one verified case of BCG-osteomyelitis and four other cases with suspected BCG-etiology. Moreover, a tabulation of 13 literature-reported cases of BCG-osteomyelitis and -osteoarthritis verified by culture is made.
2. The diagnostic difficulties are underlined. BCG-etiology ought to be suspected when the infection seems to be of low virulence, when antibiotic treatment gives no signs of regression after some weeks, and when less than 4 years have elapsed since the child has been BCG-vaccinated.
3. Bacteriological culture is positive only in about 1 of 5 cases.
4. The prognosis is good but there is a risk of joint deformity and growth disturbances in the affected bone.
5. The frequency of verified and suspected cases of BCG-osteomyelitis and/or -osteoarthritis in Sweden is estimated to be at least 1:80,000 in BCG-vaccinated children.
6. The question of a possible predisposing, maybe temporary, immunological defect is discussed.

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