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Disseminated Bacille Calmette-Guérin infection at a glance: a mini review of the literature

Abstract

Introduction: Immunodeficient children are at a high risk of disseminated Bacillus Calmette-Guérin [BCG] infection. We assessed the literature on clinical manifestations of BCGosis in children with specific primary immunodeficiencies.
Material and methods: We conducted a systematic review of clinical practice articles by searching Medline, PubMed, Embase, Scopus, Web of Science and Google Scholar from their inception to date.
Results: Thirty-seven articles were included regarding BCG vaccination and its dissemination in children with primary immunodeficiencies. Articles on dissemination after intravesicular BCG were excluded from the study.
Conclusions: Since disseminated BCG vaccination may be the first manifestation of a primary immunodeficiency disease, a comprehensive search for immunological defects in children developing these problems after BCG vaccination seems rational.

Key words: BCG, immunization, disseminated BCG infection, BCGosis, BCGitis

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Introduction

Considering that tuberculosis affects about one-third of the world's population and is the leading infectious cause of death in the world, immunization with Bacille Calmette-Guérin (BCG) is recommended to protect children against tuberculosis [1]. BCG immunization with a live attenuated bacterial vaccine derived from *Mycobacterium bovis* was first used in 1921 [2, 3] as the primary prophylaxis against tuberculosis. It is the most widely administered vaccine in the world [4]. BCG immunization during the neonatal period protects at least until 5 years of age from the most severe consequences of tuberculosis (TB) [5], such as miliary tuberculosis and tuberculosis meningitis [6], and therefore, the World Health Organization (WHO) recommends vaccination in high burden countries [2]. Although safe, BCG vaccination may be associated with several complications, ranging from a regional disease called BCGitis to a disseminated disease, namely BCGosis [7, 8]. Adverse reactions are rare (up to 23.8% of cases) [9], with the most frequent one — purulent regional lymphadenitis — presenting as local swelling and erythema [4], followed by bone infection as the second most frequent complication [9]. Vaccination technique, dose and preparation of the vaccine and the BCG strain are significant risk factors [4, 10]. It has been reported that T cell counts in healthy infants may be suppressed after BCG vaccination but these quantitative changes have not been associated with functional derangements [11, 12]. Disseminated BCG infection, a lethal event in 50 to 71% of cases, is somewhat rarer with an estimated incidence

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of 0.1 to 4.3 per one million vaccinated children [9, 13]. Immunocompromised patients are not only susceptible to mycobacterial diseases, but also to the BCG vaccine complications [8]. These individuals may experience dissemination of the bacilli due to their underlying immunological defects. Disseminated BCG infection has been reported in severe combined immunodeficiencies [SCID], chronic granulomatous disease (CGD), complete DiGeorge syndrome and mandelian susceptibility to mycobacterial disease (MSMD) with underlying genetic defects [9].

The aim of this study is to evaluate the most frequent clinical manifestations of disseminated BCG infections in vaccinated children with unidentified primary immunodeficiencies at the time of neonatal immunization.

Material and methods

We conducted a systematic review of scientific medical literature (Medline, PubMed, Embase, Scopus, Web of Science and Google Scholar), i.e. articles published in English on the clinical manifestations of disseminated BCG infection, with no time limitation — from the inception of the databases to date. BCG complications, BCGitis, BCGosis, and disseminated BCG infection were searched through the literature. We used free texts and their related articles to search PubMed, ISI Web of Science and EMBASE. More than 50 published articles from all over the world, including original articles, review articles and case reports were used. All the articles on disseminated BCG infection following intravesicular BCG were excluded from the study.

Discussion

The aim of the article is to review the associated signs of disseminated BCG infection in addition to the clinical manifestations of the specific underlying immunodeficiency disorder. BCG vaccination may be associated with variable local and systemic complications. Disseminated BCG infection, although rare, is a devastating complication of inadvertent BCG immunization in immunocompromised children. The most common immunodeficiencies connected with the dissemination of BCG following immunization include SCID, MSMD, CGD, DiGeorge, common variable immunodeficiency (CVID), NF-kappa B essential modulator (NEMO), tyrosine kinase 2 (TYK2) and human immunodeficiency virus [14] infection. Surprisingly, BCG dissemination has also been reported as a rare event in a case of CVID [15, 16]. Previous studies comparing disseminated BCG infection in SCID and CGD reported that many CGD patients are more prone to cure with the anti-TB regimen in contrast to the SCID patients [8, 17–19]. CGD patients are more likely to present with lymphadenitis [8, 20]. MSMD is a clinical phenotype, extending beyond mycobacterial diseases which should be considered in all patients presenting with nontuberculous mycobacterial infections such as *Mycobacterium bovis* [21]. The subjects who develop mycobacterial disease caused by BCG, environmental mycobacteria (EM) and *M. tuberculosis* are typically resistant to other infections except salmonella [22]. By contrast, patients with CGD are less susceptible to EM [22]. The median age of onset of BCGosis reported by Ying *et al.* and Al-Hojaj *et al.* in their studies were 3.6–4 months [23, 24]. BCG-induced disease phenotypes were designated in 2006 by Hesseling *et al.* as a local, regional, distant or disseminated pattern with the two first conditions known as BCGitis and the latter two identified as BCGosis [25]. Definitive disseminated BCG infection is diagnosed basing on the existence of systemic symptoms such as fever, malaise, fatigue, weight loss or stunted growth and two or more areas of involvement beyond the BCG vaccination site, in addition to identification of *Mycobacterium bovis* BCG strain by culture and/or standard polymerase chain reaction (PCR), as well as histopathologic changes with granulomatous inflammation. Areas of involvement may include skin papules, nodules, or ulcers; lymphadenitis; lung infection; liver or spleen enlargement; osteomyelitis; mechanical obstructions of the respiratory or gastrointestinal tracts; malabsorption of nutrients and diarrhea [21]. Finding similar clinical manifestations as mentioned above through identification of *Mycobacterium tuberculosis* complex by PCR, without differentiation of *Mycobacterium bovis* BCG substrain or other members of the *Mycobacterium tuberculosis* complex and negative mycobacterial cultures, with the presence of typical histopathologic changes with granulomatous inflammation is indicative of probable disseminated BCG infection [13]. Historically, this is a disease of infants and young children [26]. Casanova in 1995 reviewed 121 published case reports of disseminated BCG infections and found 61 cases of definitive immunodeficiency among them [27]. Initial presentation includes usually local erythema preceding progressively enlarging swelling at axillary region ipsilateral to the

injection site, accompanying pus discharge. Intermittent fever, generalized lymphadenopathies, hepatosplenomegaly, cough, bone involvement, weight loss and skin rash may develop later in the course of the disease [15, 26]. Refractory cough due to recurrent lower respiratory infections is another presentation of the disease reported in several cases [28], without significant changes in chest radiography [4]. Osseous involvement is another finding in disseminated BCG infection [6]. Hemophagocytic lymphocytic histiocytosis (HLH) is a rare complication of the disease [29].

Lymphadenopathies are the most common presenting features of the disease involving axillary, cervical, mediastinal, retroperitoneal, mesenteric and inguinal regions usually with a slow resolution after treatment [4]. In contrast to tuberculosis, which may present with inflammatory conglomerations of bowel loops with adherent omentum and adjacent lymphadenopathy, this finding is not a common feature in children with disseminated BCG infection [30].

Pulmonary involvement is usually associated with pulmonary symptoms, including chronic cough with intermittent fever. Plain radiography or CT scan of the chest may reveal pneumonic infiltration [22] and hilar/mediastinal lymphadenopathies. Pulmonary nodularity may occur due to the disseminated BCG disease.

Skeletal involvement may affect the hands, arms, legs, vertebrae and orbit. BCG osteomyelitis usually occurs in the epiphysis and metaphysis and can cross the growth plate with soft tissue swelling around the affected bone [31].

Hepatic and splenic lesions with variable sizes most commonly presenting as numerous small nodules detected by imaging modalities, including ultrasound evaluation or CT scan have been reported in patients with disseminated BCG infection [4].

Disseminated BCG infection is extremely difficult to treat as there is a low chance of complete eradication of the microorganism [32].

A key point in treating disseminated BCG infections is to identify the culprit organism as soon as possible to start appropriate antibiotics [33]. However, in the patients with compatible clinical signs and symptoms, suspected of primary immunodeficiencies, a positive acid-fast bacilli smear is sufficient for anti-TB treatment to be initiated promptly, with no delay to obtain the PCR results or cultures [34].

While there are no clear guidelines on the best mode of treatment for disseminated BCG infection, aggressive therapy involving at least four anti-TB drugs [including isoniazid, rifampicin and ethambutol plus an additional agent such as quinolone, aminoglycoside and clarithromycin] are usually initiated until complete recovery [32, 35, 36]. Then, the treatment is continued with a two-drug prophylactic regimen. Prolonged use of these drugs may cause organ toxicities and drug resistance [32], which necessitates treatment modification [36]. Because of the BCG resistance to pyrazinamide, there is no place for this drug in the treatment protocol of these children [37]. Low-level isoniazid resistance to Connaught strains has been reported in Denmark [36]. During the treatment period, close follow-up and observation of the patients is essential for reviewing the regimen when the culture and sensitivity results become available [36].

IFN-γ is an effective modality of treatment in addition to anti-TB drugs in treating patients with MSMD and CGD [11].

Whenever possible and available, hematopoietic stem cell transplantation (HSCT) is another treatment option for these children [37]. However, post-transplant inflammatory complications developed upon immune reconstitution may necessitate immune suppression which not only may affect immune recovery but also may increase the risk of opportunistic infections [32].

Unfortunately, disseminated BCG disease is one of the most common causes of death in patients with primary immunodeficiency diseases due to clinical and conventional diagnostic delay [34].

Conclusions

A history of parental consanguinity and serious recurrent infections or death in other family members are two important risk factors that should be considered before BCG vaccination. Practically, family history awareness of vaccine-related complications should be promoted in antenatal visits to induce further detailed evaluations and counseling in a sufficient period of time. Since disseminated BCG vaccination may be the first manifestation of a primary immunodeficiency disease which may lead to death later in the life, a comprehensive search for immunological defects in children developing these problems after BCG vaccination seems rational.

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