Disseminated Bacillus Calmette-Guérin and Susceptibility to Mycobacterial Infections—Implications on Bacillus Calmette-Guérin Vaccinations

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Abstract

Bacillus Calmette-Guérin (BCG) is a live vaccine and has the potential to cause local disease and systemic dissemination in immunocompromised hosts, including infants who are infected with human immunodeficiency virus (HIV) through vertical transmission, and patients with primary immunodeficiencies (PID) such as severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD), hyper-IgM syndrome, and defects of the IL12-IFNγ axis (Mendelian susceptibility to mycobacterial diseases, MSMD). Disseminated BCG is extremely difficult to treat. The chance of complete eradication is low unless functional immune response is restored by haematopoietic stem cell transplant. Prolonged use of anti-mycobacterial drugs often causes organ toxicities and drug resistance. Inflammatory complications which develop upon immunoreconstitution post-transplant may necessitate immunosuppressive treatment, which adversely affect immune recovery and increases risks of opportunistic infections. Multiple BCG reactivations can occur in patients with CGD and MSMD, and BCG can remain latent until reactivations take place in adulthood and manifest as disease. It is important for neonatologists, general practitioners, primary care clinicians and nurses working in maternal and child care centers to be aware of BCG-related complications, which may be the first sign of an underlying immunodeficiency. As neonatal BCG is included in standard vaccination schedule in many countries, it is a challenge to identify and avoid administration of BCG to infants who potentially have PIDs. Deferring BCG vaccination is recently advocated to protect highly vulnerable populations, but the appropriate strategy is yet to be determined. Newborn screening for SCID offers a potential to avoid this complication, if an integrated system of screening and vaccination can be organised.

Key words: BCG, Newborn screening, Primary immunodeficiency

Introduction

Tuberculosis (TB) is endemic in Asia. Out of 22 countries with high TB burden, 10 are Asian countries.1 Bacillus Calmette-Guérin (BCG) vaccine is one of the world’s most widely used vaccine. It is a live vaccine made from attenuated strains of Mycobacterium bovis (M. bovis). BCG vaccine has consistently shown high efficacy against childhood tuberculous meningitis and miliary TB, while efficacy against adult pulmonary TB and other mycobacterial diseases is more variable. In a study performed by Trunz et al, it was estimated that 100 million doses of BCG vaccine given to children every year prevent about 40,000 cases of TB meningitis and miliary TB before these children reach their fifth birthdays, or roughly 1 case prevented for every 2500 inoculations. In particular, the numbers of cases prevented would be highest in Southeast Asia (46%), compared with 27% in sub-Saharan Africa and 15% in the Western Pacific region.2 The coverage rate of BCG vaccine in Southeast Asia and Western Pacific is 88% and 97%, respectively.3

Common Complications after BCG Inoculation

In most countries, BCG vaccine is administered to neonates soon after birth by intradermal inoculation, typically over the left upper deltoid region. Inoculation site reaction commonly begins with an erythematous induration of 5 mm to 15 mm, followed by formation of a bluish-red...
Disseminated BCG

The estimated incidence of disseminated BCG is 1 to 3.4 per million.9-11 Distant BCG, defined as involvement of any site beyond a local or regional ipsilateral process, includes any of the following: BCG confirmed from at least 1 distant site beyond the vaccination site e.g. pulmonary secretions (gastric aspirate, tracheal aspirate), cerebrospinal fluid, urine, osteitis and distant skin lesions.10 The diagnostic criteria for disseminated BCG as defined by the European Society for Immunodeficiency (ESID) can be found on the ESID website.12 Distant and disseminated BCG should be regarded as an indicator for underlying immunodeficiency until proven otherwise. The estimated incidence of disseminated BCG in HIV-infected babies who receive BCG vaccination is nearly 1/100.13 If HIV is excluded, primary immunodeficiency disorders (PIDs) should be suspected.

Disseminated BCG in Patients with Primary Immunodeficiencies

Innate immunity, particularly phagocytic oxidase activity and the interleukin-12/interferon-gamma (IL-12/IFN-γ) axis, as well as T-cell immunity are crucial in protective immune response against mycobacteria. PIDs which are associated with disseminated BCG include severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD), X-linked hyper-IgM syndrome (CD40 ligand deficiency) and Mendelian susceptibility to mycobacterial diseases (MSMD).14 The clinical features and laboratory findings are listed in Table 1.

Disseminated BCG: Clinical Features

All infants presenting with BCG complications should be thoroughly examined for signs of distant or disseminated disease. Clinicians should look for enlarged lymph nodes in the neck, supraclavicular region and groin. The liver and spleen are often enlarged in disseminated disease. Abnormal respiratory signs may suggest pulmonary involvement, and chest x-ray should be performed to look for abnormal opacities or infiltration. Dissemination to skin often manifest as erythematous papules or indurations (Fig. 1a). Bone involvement may present as swelling or tenderness. Osteolytic lesions may be seen on the x-ray (Fig. 1b), and the extent can be evaluated by bone scan. Bone marrow involvement should be suspected if there is anaemia, and a microbiologist should be consulted as special culture medium and prolonged culture is required to maximise the yield of BCG. One should carefully examine for neurological deficits, and brain imaging and lumbar puncture should be performed to exclude BCG meningitis.

Infants with disseminated BCG are often susceptible to other infections, and the clues to the possibility of an underlying PID may be identified by thorough physical examination. First, they often fail to thrive as a result of repeated episodes of infection and poor feeding. Mucocutaneous candidiasis is suggestive of T-cell deficiency or gain-of-function STAT1 defect. In addition to BCG, infants with SCID are susceptible to Pneumocystis jiroveci pneumonia (PCP), viral (respiratory viruses and cytomegalovirus) and fungal pneumonia (Aspergillus), and bronchoalveolar lavage should be considered for microbiological documentation. Patients with CGD often have pyogenic infection such as perianal abscess, lymphadenitis, osteomyelitis and hepatosplenic abscess.

Immune Evaluation for Infants with Disseminated BCG

While definitive diagnosis of PIDs may require sophisticated functional and molecular studies, a significant proportion of PIDs can be picked up by simple tests such as full blood count and serum immunoglobulin levels. The fact that absolute lymphocyte count (ALC) <2.5 × 10⁹/L is abnormal in infants is often under-recognised. An infant presenting with recurrent infections and failure to thrive with lymphopenia on multiple occasions, together with absent thymic shadow on chest x-ray should lead to a high suspicion of SCID.15 Early referral to immunologists for diagnostic evaluation is essential, and this has a significant impact on the survival and prognosis of PIDs. Timely commencement of treatment will prevent organ damage and preserve the best outcome for patients whose disease is amenable to cure by haematopoietic stem cell transplant (HSCT).

Basic immune evaluation includes lymphocyte subset for enumeration of T-cells, B-cells and NK-cells, immunoglobulin levels (IgG, A, M) as well as evaluation of neutrophil oxidative burst by nitroblue tetrazolium test (NBT) or dihydrorhodamine test (DHR). Functional analysis of the IL12-IFNγ axis is only available in specialised...
Table 1. Clinical and Immunological Features of Primary Immunodeficiency Predisposing to BCG Disease

<table>
<thead>
<tr>
<th>PID</th>
<th>Inheritance</th>
<th>Infections Other Than BCG Disease</th>
<th>Non-infective Manifestations</th>
<th>Immunological Investigations</th>
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| Severe combined immunodeficiency | X-linked: IL2RG deficiency  
Autosomal recessive:  
T-B+ SCID: e.g. JAK3, IL7R  
T-B- SCID: e.g. RAG1, RAG2, Artemis, LIG4  
ADA deficiency  
Complete DiGeorge syndrome  
Cartilage hair hypoplasia | Bacterial sepsis  
Respiratory viruses (RSV, parainfluenza, influenza)  
CMV, EBV  
Fungal: mucocutaneous candidiasis, candidemia, aspergillosis  
Pneumocystis jiroveci pneumonia  
Complications associated with other live vaccines: rotavirus, varicella zoster, oral polio vaccine | Autoimmunity associated with Omenn syndrome (leaky SCID)  
Maternal engraftment syndrome resulting in graft-versus-host disease  
Dysmorphism in some forms of SCID e.g. cartilage hair hypoplasia, LIG4 deficiency | IgG/A/M  
Lymphocyte subset  
Lymphocyte proliferation  
Measures of thymic output: naïve T-cells, TREC  
Molecular confirmation: Flow cytometry for protein expression (e.g. γc, JAK3, IL7R)  
FISH for 22q11.2 deletion  
Genetic test |
| Chronic granulomatous disease    | X-linked: CYBB deficiency  
Autosomal recessive:  
e.g. CYBA, NCF1, NCF2 | Bacterial sepsis (e.g. S. aureus, E. coli, Salmonella, Klebsiella, Pseudomonas)  
Nocardia, Serratia, Aspergillus, Burkholderia cepacia, B. pseudomallei | Granuloma formation | Nitroblue tetrazolium test or dihydrorhodamine test  
Genetic test |
| Mendelian susceptibility to mycobacterial diseases | Autosomal recessive:  
IL12B, IL12RB1, IFNGR1, IFNGR2, loss-of-function STAT1, NEMO, TYK2 | Non-tuberculous mycobacteria  
Tuberculosis  
Non-typhoidal salmonellosis | NEMO: anhidrotic ectodermal dysplasia | Functional studies of the IL12/IFN-γ axis  
Genetic test |
| Gain-of-function STAT1 defect    | Autosomal dominant | Chronic mucocutaneous candidiasis  
Invasive mycosis e.g. aspergillosis, coccidiomycosis, histoplasmosis, Penicillium marneffei  
Non-tuberculous mycobacteria  
Viral infections e.g. CMV, EBV | Autoimmunity e.g. type 1 diabetes mellitus, hypothyroidism, enteropathy | Flow cytometry for phosphorylated STAT1 expression  
Genetic test |
| CD40 ligand deficiency           | X-linked | Encapsulated bacteria  
e.g. S. pneumoniae  
Cryptosporidium  
Toxoplasma gondii  
Pneumocystis jiroveci | Autoimmunity | IgG/A/M  
CD40 ligand expression by flow cytometry  
Genetic test |

ADA: Adenosine deaminase; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; FISH: Fluorescent in situ hybridisation; RSV: Respiratory syncytial virus; SCID: Severe combined immunodeficiency; TREC: T-cell receptor excision circles

Fig. 1. Disseminated BCG in SCID patients, manifesting as erythematous skin nodules in A and osteolytic bone lesions in B. Multiple moth-eaten lesions can be seen in the metatarsal bones.
laboratories. Genetic testing provides definitive diagnosis and useful information for family screening and future prenatal diagnosis.

**Challenges in the Management of BCG Disease in Patients with PID**

It is recommended that anti-TB treatment including 4 or more anti-TB drugs should be given to patients with PID until complete recovery. Then, a prophylactic regimen with 2 drugs should be continued, until complete immunological reconstitution after HSCT is achieved. It should be noted that BCG strains are inherently resistant to pyrazinamide. Commonly used anti-BCG regimen consists of a backbone of 3 first-line anti-TB drugs (isoniazid, rifampicin and ethambutol), plus an additional agent to which BCG is also susceptible, such as quinolone (e.g. ciprofloxacin, levofloxacin), aminoglycoside (e.g. amikacin, streptomycin) and clarithromycin. Low-level isoniazid resistance was observed in the Denmark strain (SSI 1331) and Connaught strain. The regimen should be reviewed when culture and sensitivity results are available, and modified when side effects arise.

BCG disease does not only contribute to morbidity and mortality for infants prior to transplant, but also complicates post-transplant course and adversely affect recovery and quality of life. Manifestations range from fever, skin papules, ulceration and discharge from the BCG inoculation site, hepatosplenomegaly and osteomyelitis, often become more severe after transplant as the donor graft begin to mount an immune response in an attempt to clear the BCG. Enlarged intra-abdominal and groin lymph nodes can result in lymphedema. Immunoreconstitution syndrome (IRIS) presenting as fever, hypercalcaemia and renal impairment requires treatment with corticosteroid. Disseminated BCG disease is difficult to control, and surgical drainage of abscess might be needed. Drug resistance could also occur, and patients might require prolonged course of antimycobacterial treatment with potential toxicities.

**Disseminated BCG Disease—Is It Preventable?**

According to a multi-centred survey on 349 BCG-vaccinated SCID infants, 51% had BCG-associated complications and two-thirds of them had disseminated BCG, which was a 33,000-fold increased risk over the general population. In another cohort of 40 Iranian infants with SCID, the incidence of disseminated BCG was as high as 45%. In many countries, BCG is incorporated into standard neonatal vaccination schedule and infants are often vaccinated during the newborn period. Infants with undiagnosed PID might have received BCG, which would be contraindicated should their condition been known. It was advocated that careful family history should be taken prior to neonatal vaccination. Practically, the awareness of a family history of vaccine-related complications should be promoted among pregnant women in their antenatal visits, so that sufficient opportunity for detailed evaluation and counselling is possible. However, a positive family history will be present in <10% of SCID cases.

The study by Marciano et al (2014) showed that infants with SCID who received BCG beyond the first month of life had lower prevalence of BCG-associated complications compared to those vaccinated within the first month (38% vs 55%), and none of them died of BCG-related complications (0% vs 18%). It was suggested that deferring universal BCG vaccination until after 1 month of age would diminish BCG-associated complications in these vulnerable immunodeficient individuals. This is even more relevant to countries which are planning to implement newborn screening (NBS) for SCID, as it is logical to administer BCG only after NBS result is available and to exclude infants who are screened positive from BCG vaccination. Such a policy change may give rise to concerns about a decrease in coverage due to “missed opportunity” of vaccinating patients after birth and the potential increased risk of BCG-preventable diseases during the “unprotected” intervals. The counter-argument is that BCG vaccine has a documented protective effect against meningitis and disseminated TB in children, but it does not prevent primary infection and reactivation of latent pulmonary TB, which is the principal source of bacillary spread in the community.

Vaccine coverage is another potential concern. In Western Pacific, the coverage of BCG at birth (97%) is similar to the coverage of the third dose of diphtheria-pertussis-tetanus (DTP) vaccine (96%), which is a key indicator of immunisation programme performance. This implies that delaying BCG vaccination will not compromise the coverage rate in a robust public healthcare system. However, it should be noted that in Southeast Asia, the coverage of BCG vaccine at birth is 90% while that of the third dose of DTP vaccine is only 77%. The appropriate strategy to prevent administrating live vaccines to susceptible infants and yet achieving satisfactory coverage of BCG vaccine is yet to be determined.
REFERENCES


