

Clinical Profile and Outcome of Clinical BCG Disease in Infants

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Objective: To describe the clinical profile, immunological status and outcome of BCG disease in infants. **Methods:** All infants with a diagnosis of BCG disease in a period of 17 months were followed up. **Results:** Among 25 infants with BCG disease; 19 had local/regional involvement and 6 had suspected or confirmed distant/disseminated disease, Mean (range) age of presentation was 3.6 (1.5-9) months. Two of 6 infants with disseminated disease required second-line anti-tubercular treatment. One infant with confirmed disseminated disease had *INFYR1* receptor deficiency. There was no mortality. **Conclusion:** Most infants with BCG-related disease have local or regional disease.

Keywords: BCG, Lymphadenitis, Tuberculosis.

Complications of BCG vaccine are collectively known as BCG disease [1]. Local and regional complications (0.4-1/1000 vaccinees) develop irrespective of immune-competence status while distant/disseminated BCG disease is generally associated with well-defined immune-deficiencies [1,2]. An increase in the number of BCG-associated suppurative lymphadenitis has been reported in many countries in recent years [2-5]. Inherited disorders of INFY/Interleukin-12 (INFY/IL-12) axis have been increasingly reported in association with disseminated BCG disease [6,7], now known as Mendelian Susceptibility to Mycobacterial Diseases (MSMD). There is limited published data on clinical profile, outcome and immunological status of BCG disease in Indian literature. We undertook this study to describe the clinical profile, immunological status and outcome of BCG disease.

METHODS

This observational study was conducted at a tertiary care hospital from April 2012 to August 2013. All infants with clinically suspected BCG disease were included in the study and classified as local, regional, distant or disseminated disease [1]. Children who were already on Anti-tubercular treatment (ATT) were excluded. Strain, dose and timing of BCG vaccine were documented. Fine needle aspiration cytology of the node (FNAC) and HIV antibody screening were planned in all children. Chest X-ray, gastric aspirate for Acid-fast bacilli (AFB) and mycobacterial cultures were performed on Infants with systemic symptoms and signs of distant disease. They were evaluated for underlying primary

immunodeficiency by performing immunoglobulin assay, lymphocyte subset flow-cytometry, and neutrophil functions. If feasible, INFY/IL-12 axis defect assay was offered. Treatment was given as per protocol [1]. Local and regional diseases (non-suppurative adenitis) were observed and followed up. Infants with suppurative adenitis were subjected to therapeutic aspiration/surgical excision. They were clinically followed up for signs of dissemination.

Infants with suspected or confirmed distant/disseminated disease received ATT [2 months of Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Ofloxacin and 7 months of Isoniazid, Rifampicin, Ethambutol and Ofloxacin (2HRZEO/7HREO)] [1].

RESULTS

Twenty-five children were diagnosed with BCG disease during the study period. Nineteen children (76%) presented with local/regional disease alone and 6 (24%) with both local/regional disease and suspected or confirmed distant/disseminated disease. All infants were vaccinated in neonatal period. Nine out of 25 had received BCG vaccination in the study hospital with 0.1 mL of Danish 1331 strain. The mean (range) age of presentation was 3.6 (1.5-9) months. All these children were negative for HIV by ELISA.

Of the 25 infants, 2 had local disease that healed spontaneously. Out of 23 babies with regional lymphadenitis, suppuration occurred in 13 (57%) infants. Six of 13 infants required excision for failed aspirations. Among 4 of 9 infants with non-suppurative nodes, nodes regressed in a mean period of 7 months.

WHAT THIS STUDY ADDS?

- Three-fourth infants with BCG-related disease have regional or localized involvement and one-fourth have disseminated disease.

Six infants were classified clinically as suspected distant/disseminated disease at the onset. Signs of dissemination were noted at presentation in one and after a gap of 2-5 months in the rest. Hepato-splenomegaly (5) and failure to thrive (4) were common features. Gastric aspirate yielded positive AFB in 3 infants. *M. bovis* was isolated from blood in one infant (confirmed disseminated disease) and from gastric aspirate in another infant (confirmed distant disease). Both these infants were products of second degree consanguinity. All infants had normal immunoglobulin assays, flow cytometry and neutrophil functions. Genetic analysis of the infant with confirmed disseminated disease revealed a novel homozygous mutation in *IFN γ -R1* gene at P130H location. All these six infants received initially 2HRZEO/7HREO; four among 6 responded over 2-3 months. The mean duration of follow-up after treatment completion was 7 months with no recurrences. Though infants with confirmed distant/disseminated disease showed adequate response initially, they developed skeletal tuberculosis and increasing organomegaly over after 4-6 months. Currently, they are stable on amikacin, azithromycin and linezolid.

DISCUSSION

In the series, three-fourth of infants having BCG disease had local or regional involvement. All six children with suspected distant/disseminated BCG disease had normal immunological work-up; *IFN γ -R1* gene mutation was documented in one infant. Hesseling, *et al.* [1] reported dissemination in 32% of their infants with BCG disease [1]. They demonstrated HIV infection in 68% infants [1]. None of our infants were HIV-positive, similar to a report from Iran [9]. Primary immune-deficiencies like severe combined immune-deficiency and chronic granulomatous disease were diagnosed in 25-50% of children in these studies [1,8], but none in our study population.

Treatment of BCG disease is challenging as it is complicated by inherent resistance to Pyrazinamide and partial resistance to INH [1]. Resistance to INH was documented in two of our isolates compared to 75% in the Saudi Arabian study [2]. We followed protocol of 2HRZEO, 7 HREO and found good results [1]. Various second-line drugs like aminoglycosides, linezolid, and ethionamide have been used for resistant disease [9].

TABLE I PROFILE OF INFANTS WITH DISTANT/DISSEMINATED DISEASE

Features	No.
*Age at presentation of lymphadenopathy	4.2 mo (-1.72)
*Age at presentation of dissemination	7.1 mo (- 2.2)
Hepatosplenomegaly	5/6
Failure to thrive	4/6
Fever	3/6
Distant lymphadenopathy	3/6
Sibling death with similar presentation	2/6
Positive gastric AFB	3/6
<i>M. bovis</i> culture from gastric aspirate	1/6
<i>M. bovis</i> culture from blood	1/6

*Mean (SD).

Two of our infants were prescribed amikacin, azithromycin, and linezolid with good response. Mortality rate among distant/disseminated disease can be as high as 60-80 % [1,9].

Our study has potential limitations. Though we described 25 infants with BCG disease, we could not comment on true incidence and trend as it was a hospital-based study, and we have no previous data to compare with. Notification of adverse effects to BCG vaccine is also not strictly followed. Duration of follow-up is also short to comment on complex response, recurrence and mortality.

We conclude that most infants with BCG disease have regional or localized disease but should be followed up for development of any disseminated disease.

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