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A Study on Outcome of Clinical BCG Disease in relation to Clinical Profile in Infants in Tertiary Care Centre, Bhagalpur.

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ABSTRACT **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 20 months were followed up.
Results: Among 50 infants with BCG disease; 38 had local/regional involvement and 10 had suspected or confirmed distant/disseminated disease, Mean (range) age of presentation was 3.6 (1.5-9) months. Four of 10 infants with disseminated disease required second-line anti-tubercular treatment. One infant with confirmed disseminated disease had INFγ R1 receptor deficiency. There was no mortality.
Conclusion: Most infants with BCG- related disease have local or regional disease.

KEYWORDS : Clinical Profile, Tuberculosis, BCG, Lymphadenitis.

INTRODUCTION

Tuberculosis infection and disease among children are much more prevalent in developing countries, where resources for control are scarce. It is estimated that in developing countries the annual risk of tuberculosis infection in children is 2- 5 per cent. Widespread coverage with BCG vaccine has possibly led to modification in the pattern of clinical manifestations. It has been suggested that BCG vaccination is responsible for decrease in the occurrence of disseminated and severe disease. Localized forms of illness, e.g., intrathoracic lymphadenopathy, and localized CNS disease have been reported to occur with greater frequency [1] but these need confirmation from large epidemiological studies. Complications of BCG vaccine are collectively known as BCG disease [2]. 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 [2,3]. An increase in the number of BCG-associated suppurative lymphadenitis has been reported in many countries in recent years [3-6]. Inherited disorders of INFγ/Interleukin-12 (INFγ/IL-12) axis have been increasingly reported in association with disseminated BCG disease [7,8], 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 February 2015 to September 2016. All infants with clinically suspected BCG disease were included in the study and classified as local, regional, distant or disseminated disease [2]. 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, INFγ/IL-12 axis defect assay was offered. Treatment was given as per protocol [3]. 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)] [2].

RESULTS:

Fifty children were diagnosed with BCG disease during the study period. Thirty Eight children (76%) presented with local/regional disease alone and 12 (24%) with both local/regional disease and suspected or confirmed distant/disseminated disease. All infants were vaccinated in neonatal period. Eighteen out of 50 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 50 infants, 4 had local disease that healed spontaneously. Out of 46 babies with regional lymphadenitis, suppuration occurred in 26(57%) infants. Ten of 26 infants required excision for failed aspirations. Among 8 of 18 infants with non-suppurative nodes, nodes regressed in a mean period of 7 months. Ten 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 4 infants. M.bovis was isolated from blood in Two infants (confirmed disseminated disease) and from gastric aspirate in another infant (confirmed distant disease). Four of 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 IFNγ-R1 gene at P130H location. All these Ten infants received initially 2HRZEO/7HREO; six among 10 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 present study, 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; IFNγ-R1 gene mutation was documented in one infant. Hesseling, et al. [2] reported dissemination in 32% of their infants with BCG disease [2]. They demonstrated HIV infection in 68% infants [2]. None of our infants were HIV-positive, similar to a report from Iran [10]. Primary immune-deficiencies like severe combined immune-deficiency and chronic granulo-matous disease were diagnosed in 25-50% of children in these studies [2,9], 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 [2]. Resistance to INH was documented in two of our isolates compared to 75% in the Saudi Arabian study [3]. We followed protocol of 2HRZEO, 7 HREO and found good results [2]. Various second-line drugs like aminoglycosides, linezolid, and ethionamide have been used for resistant disease [10].

TABLE 1- Profile of Infants with distant/disseminated disease

Features	No.
*Age at presentation of lymphadenopathy	4.2 month(-1.72)
*Age at presentation of dissemination	7.1 month(-2.2)

Failure to thrive	6/10
Hepatosplenomegaly	8/10
Distant lymphadenopathy	5/10
Fever	5/10
Positive gastric AFB	4/10
M. *bovis* culture from blood	2/10
M. *bovis* culture from gastric aspirate	2/10

*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 % [2, 10]. Our study has potential limitations. Though we described 50 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.

In our study we found that most of the infants with BCG disease have regional or localized disease but should be followed up for development of any disseminated disease.

REFERENCES

1. Udani PM. BCG vaccination in India and tuberculosis in children: newer facets. Indian J Pediatr. 1994; 61 : 451-62.
2. Hesseling AC, Rabie H, Marais BJ, Manders M, Lips M, Schaaf HS, et al. Bacille Calmette Guerin vaccine induced disease in HIV infected and HIV uninfected children. Clin Infec Dis. 2006;42:548-58.
3. Bukhari E, Alzahrani M, Alsubaie S, Alrabiaah A, Alzamil F. Bacillus Calmette Guerin lymphadenitis: A six year experience in two Saudi hospitals. Indian J Pathol Microbiol. 2012;55:202-5.
4. Alrabiaah AA, Alsubaie SS, Bukhari EI, Gad A, AlzamelFA. Outbreak of Bacille Calmette Guérin-related lymphadenitis in Saudi children at a university hospital after a change in the strain of vaccine. Ann Saudi Med. 2012;32:4-8.
5. Irish Medicines Board. BCG vaccine SSI and severe local reactions. Available from: http://www.imb.ie/images/ uploaded/documents/BCG%20vaccine%20SSI%20and %20severe%20local% 20reactions.pdf. Accessed January 25, 2014.
6. Reports of lymphadenitis Following Administration of BCG Vaccine SSI. Health Science Authority. Singapore Government 2011. Available from: http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/product_safety_alerts/safety_alerts_2011/reports_of_lymphadenitis.html. Accessed January 15, 2014.
7. Elloumi-Zghal H, Barbouche MK, Chemli J, Bejaoui M, Harbi A, Snoussi N, et al. Clinical and genetic heterogeneity of inherited autosomal recessive susceptibility to disseminated mycobacterium bovis Bacille Calmette Guerin Infection Infect Dis. 2002;185:1468-75.
8. Caragol I, Casanova JL. Inherited disorders of the interleukin-12/Interferon gamma axis: Mendelian predisposition to mycobacterial disease in man. Inmunologia. 2003;22:263-76. Govindarajan KK, Chai FY. BCG adenitis – Need for increased awareness. Malaysian J Med Sci. 2011;18:66-9.
9. Paiman SA, Siadati A, Mamishi S, Tabatabaie P, Khotaee G. Disseminated Mycobacterium bovis infection after BCG vaccination. Iran J Allergy Asthma Immunol. 2006;5:133-7.
10. Ritz N, Tebruegge M, Connell TG, Sievers A, Robins – Browne R, Curtis N. Susceptibility of Mycobacterium bovis BCG vaccine strains to anti tuberculous antibiotics. Antimicrob Chemotherapy. 2009;53:316-18.