Original Article

Impact of Bacille Calmette-Guérin Vaccination on Neuroradiological Manifestations of Pediatric Tuberculous Meningitis

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Mohammad Wasay, MD, FRCP, FAAN[1], Saad Ajmal, MBBS[1], Ather M. Taqui, MBBS[1], Najam Uddin, MBBS[1], Iqbal Azam, MSc[2], Yousuf Husen, FCPS[3], and Syed Qamaruddin Nizami, FCPS[4]

Abstract

The authors conducted this study to identify whether bacille Calmette-Guérin (BCG) vaccination leads to an altered spectrum of neuroimaging findings outcome in pediatric patients with tuberculous meningitis. This retrospective study was conducted through chart review and review of computed tomography (CT) scans and magnetic resonance imaging (MRI) of patients with confirmed central nervous system tuberculosis from the year 1992 to 2005, at a large tertiary care hospital in Karachi, Pakistan. A total of 108 pediatric patients with tuberculous meningitis were included in the analysis. Of the 108 patients, 63 (58.3%) were male and 45 (41.7%) had received bacille Calmette-Guérin vaccination. There was no difference in terms of severity of clinical presentation and outcome between vaccinated and unvaccinated group. There were no significant differences in CT or MRI findings between the 2 groups except for tuberculomas on MRI, which were significantly higher in the non−bacille Calmette-Guérin vaccinated group (52.2% vs 22.7%, $P = .042$). Bacille Calmette-Guérin vaccination appears to translate into less tuberculoma formation on MRI.

Keywords

tuberculous meningitis, bacille Calmette-Guérin vaccination, central nervous system infections, CT scan, MRI, pediatric

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Tuberculosis is one of the leading causes of mortality and morbidity worldwide. Globally, 9.2 million new cases and 1.7 million deaths from tuberculosis occurred in 2006.[1] Pakistan, a developing country in South Asia, is currently the sixth most populous country in the world with a population of 172.8 million.[2] With an estimated tuberculosis prevalence of 263 and a resulting mortality of 34 per 100 000 people per year, tuberculosis is a serious public health problem in Pakistan.[1]

Tuberculous meningitis accounts for 5% to 10% of all tuberculosis cases but is responsible for more than 40% of the deaths due to tuberculosis.[3] It is more common in children. Tuberculous meningitis has proven to be a challenging disease to diagnose and treat and has received less attention than pulmonary tuberculosis.[4]

Tuberculous meningitis has a wide variety of presentations. In a review of 214 children with tuberculous meningitis, fever was reported in 91%, vomiting in 87%, personality change in 63%, seizures in 62%, nuchal rigidity in 59%, and headaches in 58%.[5] Recent contact with tuberculosis should be elucidated; several studies have shown that between 66% and 90% of children have had a recent positive contact.[5,6] Neurological complications include cranial nerve palsies, infarcts, hydrocephalus, seizures, tuberculoma, deafness, loss of sphincter control, and spastic or flaccid paralysis. Computed tomography (CT) and magnetic resonance imaging (MRI) provide diagnostic information at presentation and when complications occur. Findings such as basal enhancement, hydrocephalus, tuberculoma, and infarction are more specific for tuberculous meningitis in children as compared to other pyogenic meningitis. Meticulous microscopy followed by culture of >5 mL of cerebrospinal fluid is recommended. Cerebrospinal fluid smears are positive for

[1] Department of Neurology, The Aga Khan University, Karachi, Pakistan
[2] Department of Community Health Sciences, The Aga Khan University, Karachi, Pakistan
[3] Department of Radiology, The Aga Khan University, Karachi, Pakistan
[4] Department of Pediatrics and Child Health, The Aga Khan University, Karachi, Pakistan

Corresponding Author:
Mohammad Wasay, Department of Neurology, The Aga Khan University, Stadium Road, Karachi 74800, Pakistan
Email: mohammad.wasay@aku.edu

acid-fast bacilli in about 10% to 20% of those with tuberculous meningitis.[7] The culture of *Mycobacterium tuberculosis* from the cerebrospinal fluid is the gold standard for diagnosis but is insensitive and slow even with modern culture techniques. Newer methods of diagnosis include commercial nucleic acid amplification assays. However, a meta-analysis showed that at the start of treatment, careful bacteriology is as good as, or better than, the commercial nucleic acid amplification assays, but molecular methods may be more useful when antituberculosis drugs have started.[8] In summary, tuberculous meningitis requires a high level of suspicion for diagnosis. Early diagnosis and prompt treatment cannot be stressed enough, as a delay in treatment results in either death or considerable neurological morbidity.[9]

The bacille Calmette-Guérin (BCG) vaccine remains the cornerstone of the World Health Organization (WHO) tuberculosis prevention program in children. Even after eight decades of use, the efficacy of the bacille Calmette-Guérin vaccine is still shrouded in controversy, with reported protective rates ranging from 0% to 80% in large epidemiological studies.[10-12] The effect is probably time limited because vaccination during infancy does not decrease the incidence of tuberculosis in adults. Although the bacille Calmette-Guérin vaccination is not highly effective in preventing the illness, it does play a role in reducing the severity of the more serious forms of the disease such as disseminated disease and tuberculous meningitis.[13,14] There are no reliable data on bacille Calmette-Guérin coverage in our country, but it is estimated to be about 30%. Although the bacille Calmette-Guérin vaccine is a compulsory vaccine in Pakistan and is included in the national vaccination program, the coverage is not satisfactory. This is a reality in developing countries. For example, in the study by Yaramis et al on 214 cases with pediatric tuberculous meningitis, only 25 patients (12%) had a history of single bacille Calmette-Guérin vaccination.[5] The other children did not receive bacille Calmette-Guérin vaccination. This is despite the presence of bacille Calmette-Guérin vaccination in the routine immunization program of the Turkish Ministry of Health. It is given as an intradermal injection during the neonatal period, ideally within the first week after birth.

It is well known that the prognosis of central nervous system tuberculosis is worse in unvaccinated patients.[15-17] Adult patients with intracranial tuberculoma carry a poor prognosis as compared to nontuberculoma patients.[18] It is still unclear whether the bacille Calmette-Guérin vaccine has any influence in modifying the radiological features in pediatric patients with tuberculous meningitis. Only a few studies have explored this area and have ascertained a clinical and laboratory profile of such patients. However, neuroimaging findings have not been studied in depth: only CT scan findings have been looked at in these studies but not MRI findings. If bacille Calmette-Guérin vaccination does change the clinical and imaging spectrum of tuberculous meningitis, it is useful to identify the new features for prognosis of these patients. We conducted this study to identify whether bacille Calmette-Guérin vaccination leads to an altered spectrum of neuroimaging findings in pediatric patients with tuberculous meningitis and whether unvaccinated patients had a more severe form of intracranial tuberculosis as compared to vaccinated patients.

Methods

This retrospective study was conducted at the Aga Khan University Hospital, a large tertiary care hospital in Karachi, the largest city of Pakistan. Aga Khan University Hospital receives patients from all over Karachi. A data questionnaire was used to collect data via a thorough chart review of patients from the year 1992 to 2005. The patient records were identified by the *International Classification of Diseases, Ninth Revision* coding system. The study protocol was approved by the Institutional Ethics Review Committee. Retrospective chart reviews do not require informed consent for enrollment in a specific study at our institution. All patients or attendants sign a consent form at the time of admission permitting data to be used for research without exposing the identity of the patient. Authors have nothing to disclose as a conflict of interest. No funding was involved. All authors contributed in data analysis, manuscript writing, and manuscript review.

All patients with tuberculous meningitis aged 18 years and below were included. The criteria for tuberculous meningitis diagnosis were as follows: (1) either positive cerebrospinal fluid culture or positive biopsy (histopathology) of intracranial lesion or (2) abnormal cerebrospinal fluid or intracranial lesion with culture-positive or biopsy-positive pulmonary or nodal tuberculosis. All the patients were admitted to the hospital and underwent most laboratory and imaging studies in the same hospital. Two radiologists were involved in reviewing the imaging scans. Neuropathology (excisional biopsy) specimens were reviewed by 2 trained pathologists. The diagnosis of tuberculoma was based on the presence of caseation necrosis with granuloma formation. Specimens were stained by routine hematoxylin and eosin stain and special stains such as Ziehl-Neelson stain for acid-fast bacilli and periodic acid Schiff stain for fungal hyphae. All tuberculomas were graded for the amounts of fibrosis, gliosis, necrosis, and the cellular elements (lymphocytes, macrophages, and plasma cells). Either a documented history of bacille Calmette-Guérin vaccination or the presence of the bacille Calmette-Guérin scar were accepted as confirmation of bacille Calmette-Guérin vaccination, as few people in Pakistan keep a vaccination record. Cerebrospinal fluid cultures were performed using Lowenstein Jensen medium and BACTEC medium and recently mycobacteria growth indicator tubes medium. None of the patients underwent gastric aspirates culture because of labor-intense acid neutralization techniques and poor yield at our center.

Data were entered and analyzed using the Statistical Package for Social Sciences 16.0 (SPSS, Inc, Chicago, Illinois). Descriptive statistics were performed. Results were recorded as frequencies, means $\pm$ standard deviations, and P values. Univariate analysis was done using the χ^2 test and Fisher exact test for categorical variables. The independent samples t test was used for continuous variables. A P value of $<.05$ was taken as the criteria of significance for all purposes.

Results

A total of 192 potential patients were identified. In all, 84 were excluded because of an unconfirmed diagnosis, nonavailability of imaging data, and/or lack of proper documentation. A total of 108 pediatric patients with central nervous system tuberculosis were included in analysis. The diagnosis of tuberculosis was confirmed by positive cerebrospinal fluid culture ($n = 69$) or abnormal cerebrospinal fluid or intracranial lesion with

Table 1. Characteristics and Outcome of the Patients With Tuberculous Meningitis[a]

	Bacille Calmette-Guérin vaccinated			
	Yes (n = 45)	No (n = 63)	All (n = 108)	*P* Value
Age (years)	5.6 ± 4.4	6.9 ± 4.6	6.3 ± 4.6	.147
Gender				
Male	26 (57.8)	37 (58.7)	63 (58.3)	.921
Female	19 (42.2)	26 (41.3)	45 (41.7)	
Duration of first admission (days)	12.4 ± 9.5	11.8 ± 10.4	12.0 ± 10.0	.769
Involvement of other sites with TB				
Yes	10 (23.8)	10 (17.2)	20 (20.0)	.418
Clinical features at presentation				
Coma	11 (24)	14 (22)	25 (23)	.514
Seizures	19 (42)	23 (36)	42 (39)	.491
Hemiparesis	7 (16)	12 (19)	19 (18)	.860
Positive CSF culture for AFB	30 (66)	39 (61)	69 (67)	.542
Outcome at discharge				
Complete recovery	15 (33)	16 (25)	31 (29)	.09
With neurological deficits	24 (53)	36 (57)	60 (58)	.675
Death	8 (17)	9 (14)	17 (16)	.493

Note: AFB, acid-fast bacilli; CSF, cerebrospinal fluid; TB, tuberculosis.
[a] Percentages in parentheses.

Table 2. Comparison of CT Scan Findings Among Bacille Calmette-Guérin-Vaccinated Patients and Unvaccinated Patients

	History of Bacille Calmette-Guérin Vaccination			
	Yes (n = 30)	No (n = 41)	All (n = 71)	
CT Scan Findings	n (%)	n (%)	n (%)	*P* Value
Infarction	4 (13.3)	7 (17.1)	11 (15.5)	.750
Hydrocephalus	16 (53.3)	17 (41.5)	33 (46.5)	.322
Cerebritis	2 (6.7)	7 (17.1)	9 (12.7)	.285
Tuberculoma	3 (10.0)	7 (17.1)	10 (14.1)	.502
Meningeal enhancement	10 (33.3)	8 (19.5)	18 (25.4)	.186
Cerebral edema	4 (13.3)	6 (14.6)	10 (14.1)	>.999
Ventriculitis	1 (3.3)	3 (7.3)	4 (5.6)	.633
Cerebral atrophy	1 (3.3)	2 (4.9)	3 (4.2)	>.999

Note: CT, computed tomography.

culture-positive or biopsy-positive pulmonary or nodal tuberculosis (n = 39).The mean age was 6.3 ± 4.6 years and about 70% were aged 9 years or less. There was no significant difference between the mean ages of bacille Calmette-Guérin vaccinated and unvaccinated patients. Of the 108 patients, 63 (58.3%) were male and 45 (41.7%) had received bacille Calmette-Guérin vaccination. The mean duration of hospital stay at first admission was 12.0 ± 10.0 days, with no significant difference between the 2 groups. The overall outcome was not statistically different between the 2 groups. Table 1 shows the baseline characteristics, clinical and laboratory features, and outcome of the 2 vaccination groups.

Table 2 compares the CT scan findings among the bacille Calmette-Guérin vaccinated patients and the unvaccinated patients. A total of 71 patients were evaluated with a CT scan, with 30 in the bacille Calmette-Guérin vaccinated group. Of these, 55 (77%) were postcontrast scans. Overall, the most frequent finding reported was hydrocephalus (46.5%) followed by meningeal enhancement (25.4%) and infarction (15.5%). There were no significant differences between the 2 groups in terms of CT imaging findings.

Table 3 compares the MRI scan findings among the bacille Calmette-Guérin vaccinated patients and the unvaccinated patients. A total of 45 patients were evaluated with an MRI, with 22 in the bacille Calmette-Guérin vaccinated group. Of these, 38 (84%) were postcontrast scans. The rate of enhancement among these patients was 66% (mostly tuberculoma followed by meningeal enhancement and cerebritis). Overall, the most frequent finding reported was tuberculoma (37.5%) followed by hydrocephalus (31.1%) and meningeal enhancement (26.7%). There were no significant differences in MRI findings between the 2 groups except for the presence of a tuberculoma, which occurred significantly more often in the unvaccinated group (52.2% vs 22.7%, $P = .042$).

Table 3. Comparison of MRI Findings Among Bacille Calmette-Guérin-Vaccinated Patients and Unvaccinated Patients

	History of Bacille Calmette-Guérin Vaccination			
	Yes (n = 22)	No (n = 23)	All (n = 45)	
MRI Findings	n (%)	n (%)	n (%)	*P* Value
Infarction	4 (18.2)	4 (17.4)	8 (17.8)	>.999
Hydrocephalus	8 (36.4)	6 (26.1)	14 (31.1)	.457
Cerebritis	3 (13.6)	0 (0)	3 (6.7)	.109
Tuberculoma	5 (22.7)	12 (52.2)	17 (37.8)	.042
Meningeal enhancement	5 (22.7)	7 (30.4)	12 (26.7)	.559
Cerebral edema	1 (4.5)	3 (13.0)	4 (8.9)	.608
Myelitis	1 (4.5)	0 (0)	1 (2.2)	.489
Ventriculitis	1 (4.5)	0 (0)	1 (2.2)	.489
Cerebral atrophy	0 (0)	2 (8.7)	2 (4.4)	.489

Note: MRI, magnetic resonance imaging.

Discussion

The current study has documented the neuroimaging findings of bacille Calmette-Guérin vaccinated and unvaccinated pediatric patients with tuberculous meningitis. No significant differences exist between the 2 groups in terms of CT scan findings but when MRI findings are compared, tuberculomas are significantly more common in the non−bacille Calmette-Guérin vaccinated group. Our study did not show a statistically significant difference between the 2 groups in terms of severity of disease at presentation and outcome.

Two earlier studies explored the CT scan findings of bacille Calmette-Guérin vaccinated and unvaccinated patients, but none has commented on MRI findings. One study is from Turkey[16] and the more recent one is from India,[15] a South Asian developing country like Pakistan.

There were no significant differences between the ages of the bacille Calmette-Guérin vaccinated and unvaccinated patients in either of the 2 studies. This is concordant with our findings. However, the mean age of patients in both groups was higher in our study population when compared to the 2 studies: vaccinated group (5.6 years vs 3.9 [Indian] and 4.1 years [Turkish]) and unvaccinated group (6.9 years vs 3.8 [Indian] and 4.4 years [Turkish]). This implies that bacille Calmette-Guérin vaccination has no effect on the age at which tuberculous meningitis develops. However, our study indicates that tuberculous meningitis manifests itself at an older age in Pakistan, as compared to other countries. We do not have an explanation for this difference. This difference in ages could be due to sampling bias or difference in vaccination coverages or nutritional status of patients. In a study by Yaramis et al, age ranged from 3 months to 15 years, with a mean age of 4.1 years; 77% of the children were younger than 5 years and 44% of the patients were between 12 and 24 months of age.[5] Jamieson's study did not mention the mean age but only mentioned that Red Cross Children's Hospital treats children up to 12 years of age.[19] Patients in our series were older than those in Yaramis' series, which is in agreement with their observations.

Bacille Calmette-Guérin vaccination had no effect on the length of hospital stay, similar to the findings by Kumar et al.[15] Our patients' hospital stay was almost half that reported by an Indian study[15]: bacille Calmette-Guérin vaccinated group (12.4 days vs 22.3 days) and unvaccinated group (11.8 vs 20.7). One plausible explanation is that our study population presented at earlier stages of tuberculous meningitis than patients in the Indian study and hence recovered faster. Alternatively, the criteria for discharge may have been different in the Indian study.

When the CT scan findings in our study were compared to those in the 2 studies, hydrocephalus was the most common finding in all 3 studies (46.5% vs 97.9%-100% [Indian] and 63.5% [Turkish]). However, it was found in less than half the patients in our study compared to the Indian study where almost all the 150 patients had hydrocephalus. This observation suggests that the patients were sicker in the Indian study. The next most common finding in all the 3 studies was basilar meningeal enhancement (25.3% vs 81.4-84.3% [Indian] and 29.9% [Turkish]). Again, it is noted that basilar meningeal enhancement was 3 times more commonly found in the Indian study when compared to the current study.

There were no significant differences in the CT scan findings between the bacille Calmette-Guérin vaccinated and unvaccinated group. This was also the case in the Indian study, but Guler et al reported that tuberculomas were observed more frequently in the unvaccinated group ($P < .02$).[16] This study was based on CT scan findings only. One study comparing CT scan and MRI concluded that CT scans were more sensitive in diagnosing calcification, whereas MRI scans were more sensitive in picking up tuberculomas, infarcts, and meningeal enhancement.[20] Calcification is rarely seen in tuberculomas.

Intracranial tuberculomas are histologically composed of caseating granulomatous tissue and result from hematogenous spread from a systemic tuberculous infection.[3] They may occur as isolated space-occupying lesions or may coexist with tuberculous meningitis. It is reported that tuberculomas are less frequently observed in human immunodeficiency virus

(HIV)-infected patients than non-HIV-infected patients. This observation had led to the hypothesis that tuberculomas form because of a robust immunological response to tuberculous infection. A study of adult patients with intracranial tuberculoma from our center reported that multiple tuberculomas and infratentorial lesions were more common in our population as compared to previous reports.[20] In the current study, 17 (37.8%) children had tuberculomas detected by MRI on admission and 10 (14.1%) by CT scan. We did not include tuberculomas that developed as a paradoxical response after starting antituberculous therapy. The frequency of tuberculomas in children in our study is much higher than that reported in the literature: Jameison reported tuberculoma frequency as 10% in his study[19] and Yaramis et al[5] reported a frequency of 2% in their 214 cases with pediatric tuberculous meningitis. In addition, Yaramis et al reported that tuberculomas may be more common in older children, and basilar meningitis and hydrocephalus more common in younger children.

Our study did not show a statistically significant difference between the 2 groups in terms of severity of disease at presentation and outcome. We do not have a clear explanation for these findings but it is possible that vaccinated people mount a strong immunological response leading to eradication of intraparenchymal infection as compared with unvaccinated participants where infection is sealed off but not eradicated by the immune system. It is our observation that the presence of tuberculoma on imaging represents a more severe form of central nervous system tuberculosis as compared to patients with tuberculous meningitis without tuberculoma. Patients with tuberculoma have more neurological disability and require longer treatment mainly due to parenchymal involvement, while in tuberculous meningitis, the disease is largely limited to meninges. We postulate that tuberculoma formation in central nervous system tuberculosis is probably representative of a defective immune response where infection is not eradicated, but contained.

Overall, having received bacille Calmette-Guérin vaccination correlated with a lower likelihood of tuberculoma formation on MRI or less severe form of central nervous system tuberculosis. The mechanism of this decreased tuberculoma in vaccinated patients is not well understood. These findings may provide a basis for the previous findings that unvaccinated patients have a more severe form of central nervous system tuberculosis with more complications and sequelae.

A few caveats have to be borne in mind before interpreting the results of this study. The immune status of these patients, including their HIV status, was not known. About 10% to 15% of bacille Calmette-Guérin vaccinated patients do not develop scars at the injection site. In the absence of documentation of vaccination, these patients may have been included in the unvaccinated group. The quality of vaccination is also questionable in rural areas. Being a retrospective study, it had an inherent limitation; precise data about the duration of illness before presentation, Glasgow Coma Scale value, or tuberculous meningitis stage at presentation and other relevant characteristics could not be collected.

Conclusion

Bacille Calmette-Guérin vaccination appears to translate into less tuberculoma formation on MRI. There were no other significant differences found in CT or MRI scan abnormalities between bacille Calmette-Guérin vaccinated and unvaccinated group. As a whole, neuroradiological findings of tuberculous meningitis are not much affected by bacille Calmette-Guérin vaccination. Further studies with a larger sample size may be required to confirm this.

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Declaration of Conflicting Interests

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