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Utility and Cost Effectiveness of CT Scan in Diagnosis and in Taking Decisions in Neurotuberculosis in Resource Limited Setting

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ABSTRACT

Neurotuberculosis poses a significant health challenge, especially in resource-limited settings, where diagnostic tools and financial constraints can impede timely and accurate identification. This study aims to evaluate the utility and cost-effectiveness of CT scans in the diagnosis and management decisions related to Neurotuberculosis in a resource-limited setting. The study was conducted at a tertiary care teaching hospital in Vadodara, Gujarat, India, over a one-year period. Thirty-four patients, aged 6 months to 12 years, diagnosed with Neurotuberculosis, were enrolled. The study utilized the Kuppuswami method for socioeconomic classification and the British Medical Council Staging System for clinical staging. Clinical, radiological, and laboratory data were collected and CT scans were performed under cost constraints. The study explored the utility of CT scans in diagnosing and informing management decisions for Neurotuberculosis in the context of limited resources. The majority of patients belonged to socioeconomic classes III and IV. Clinical presentations included fever, convulsions, vomiting, and altered sensorium. Monteux tests, neuroimaging (CT scans), chest X-rays, and routine hematological tests were employed for diagnosis. The CT scans revealed hydrocephalus as the most common finding, and 3 out of 16 patients with hydrocephalus succumbed to the condition. The study demonstrated that CT scans were crucial for confirming the diagnosis in only 2 out of 34 cases. Moreover, clinical staging and CT findings did not significantly alter management decisions. In resource-limited settings, this study underscores the limited role of CT scans in diagnosing and managing Neurotuberculosis. While CT scans provided additional diagnostic confirmation in a small subset of cases, their routine use did not significantly impact overall management decisions. These findings highlight the importance of exploring cost-effective diagnostic alternatives and optimizing resource utilization in the context of Neurotuberculosis management in resource-limited settings.

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Key Words

Neurotuberculosis, CT scan, tuberculous meningitis, mantoux test

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INTRODUCTION

Tuberculosis (TB) remains a formidable public health challenge[1]. Latent TB affects an estimated 1.7 billion individuals globally[1]. In 2018, TB resulted in illness for 10 million people worldwide, causing the deaths of 1.2 million HIV-negative individuals and 251,000 people living with HIV (PLHIV)[1]. Extrapolating from global TB cases, approximately 14% represent extrapulmonary TB, with a pronounced prevalence in children and PLHIV[2,3]. Specifically, tuberculous meningitis comprises approximately 1% of the total global TB cases [3].

Tuberculosis (TB) primarily presents as a pulmonary ailment but extends its impact to diverse anatomical sites, leading to the manifestation of extra pulmonary TB (EPTB). Approximately 5% of all EPTB cases are attributed to tuberculous meningitis (TBM), a condition arising from the dissemination of M. tuberculosis into the meninges and cerebrospinal fluid (CSF)[4]. The precise proportion of TB cases represented by TBM remains elusive, exhibiting variability in studies contingent upon local TB prevalence. In regions characterized by a high TB burden, TB M proportions of about 10% are proposed, while low TB prevalence settings suggest proportions around 1%[5]. It is estimated that a minimum of 100,000 individuals develop TBM annually[5]. TBM predominantly afflicts young children, specifically those aged 2 to 4 years and individuals concurrently infected with the human immunodeficiency virus (HIV)[3,6].

Physicians necessitate reliance upon the clinical presentation and promptly available investigative outcomes, notably cerebrospinal fluid (CSF) biochemistry, cell counts and chest radiography[7]. While brain imaging is not obligatory for establishing a diagnosis of probable or definite tuberculous meningitis (TBM), distinct abnormalities on imaging have been documented to enhance diagnostic certainty. A recent consensus case definition (CCD), designed for research applications by experts, incorporates specific radiological indicators in TBM diagnosis, including hydrocephalus, infarcts, tuberculoma(s), basal meningeal enhancement and the presence of pre-contrast basal hyper densities[8].

Computed tomography (CT) of the brain reveals hydrocephalus and meningeal enhancement as the most sensitive signs of TBM, with reported occurrences in 80% and 75% of pediatric cases[8-10] and 45% and up to 34% of adult cases, respectively[9-11]. Although magnetic resonance imaging surpasses CT imaging in TBM diagnosis[12], its accessibility may be limited in resource-constrained settings burdened by high tuberculosis prevalence.

The establishment of well-defined criteria for tuberculous meningitis (TBM) diagnosis is imperative. Both the consensus case definition (CCD) and the previously mentioned criteria for basal meningeal enhancement hold significant potential to advance TBM research. However, it is noteworthy that these criteria have not undergone prospective evaluation. In consideration of these factors, a study was conducted on patients with tuberculous meningitis/Neurotuberculosis to assess the efficacy and cost-effectiveness of computed tomography (CT) scans in the diagnostic process. The study aimed to elucidate the role of CT scans in enhancing management-related decisions for patients admitted to a tertiary care teaching hospital in Vadodara, Gujarat, India.

MATERIALS AND METHODS

Upon receiving approval from the ethics committee, this study was executed in the Pediatric Department at Sir Sayajirao Gayakwad Hospital, Vadodara, Gujarat, India, spanning from January 2011 to December 2011.

Inclusion criteria: A total of 34 patients falling within the age range of 6 months to 12 years were enrolled in this study, all of whom presented with Neurotuberculosis, predominantly Tuberculous Meningitis. Following registration, a comprehensive assessment included the collection of detailed medical history, vaccination records and information pertaining to contact with individuals diagnosed with Kochs' (Mycobacterium tuberculosis) infection. The definition of contact encompassed individuals exposed to someone with infectious TB disease, typically involving family members, roommates or housemates, close friends, coworkers, classmates and other associates. A thorough examination was conducted, focusing on general and systemic aspects, with particular attention given to the central nervous system (CNS) examination. The clinical staging of Tuberculosis was performed following the British Medical Council Staging System. The socioeconomic classification of the study cohort was determined using the Kuppuswami method, while nutritional status was evaluated in accordance with the IAPC Classification.

The Monteux test, employing 5 Tuberculin Units (TU), was administered to all patients on the left forearm and readings were documented at the conclusion of a 72-hour period. Neuroimaging, in the form of either a CT scan or MRI, was conducted through the auspices of Rogi Kalyan Samiti or at the most economical rate (Rs.1400) available at SSG Hospital in Vadodara. Chest X-rays (CXR) were performed and interpreted by a radiologist at SSG Hospital. Standard hematological analyses, encompassing total counts (TC), differential counts (DC) and erythrocyte sedimentation rate (ESR), were routinely conducted for all patients. Lumbar puncture was executed following the elimination of contraindications. Financial constraints and limited

accessibility precluded the conduct of advanced investigations such as ADA assay, PCR, BACTET, etc. Clinical observations were systematically scrutinized and correlated with the findings obtained from CT head examinations.

RESULT

The investigation was conducted in the pediatric department of SSG Hospital, Vadodara, Gujarat, India, spanning from January 2011 to December 2011, encompassing a duration of 12 months. A cohort of 34 patients diagnosed with Neurotuberculosis was included in the study. The findings of this study revealed a marginally higher prevalence among females (52.94%) compared to males (47.06%). However, these differences did not attain statistical significance, as indicated in Table 1. The male to female ratio in this study was calculated as 0.88:1. Approximately half of the total cases under scrutiny fell within the age group of 3 years or younger.

In our investigation the classification of socioeconomic status was executed utilizing the Kuppuswami method. Predominantly, 20 patients were identified as belonging to socioeconomic class III. Given the coexistence of malnutrition, exposure to tuberculosis contact and the neglect of early symptoms associated with tuberculous meningitis (TBM), it is discernible that individuals in the lower socioeconomic class are predisposed to Neurotuberculosis, as illustrated in Table 1.

Pyrexia was the predominant complaint, reported by 94% of participants, followed by convulsions (73%), emesis (55%) and altered sensorium (47%). Other symptoms were infrequently observed. Six out of the 34 patients had a familial history of tuberculosis. Within our study cohort, three out of eight individuals who were not vaccinated and eight out of the 26 who were vaccinated, succumbed to the condition, yielding a mortality rate that was comparatively higher in the unvaccinated group. Nevertheless, due to the limited sample size, statistical significance could not be ascertained from this observation, as depicted in Table 1.

Within our investigation, 60% of the recorded mortality events, comprising 6 out of 10 cases, were concentrated in the age group of 6 years or younger, as detailed in Table 2. This elevated mortality rate in the younger age bracket suggests that lower age serves as an independent risk factor for mortality in tuberculous meningitis (TBM). Of the 34 patients with Neurotuberculosis in our study, three tested positive for the Mantoux test (MT). The prevalence of MT positivity was notably higher in stage I cases (75%) in comparison to stage II cases (25%). MT reactivity exhibited a higher occurrence in the group that survived (9%) compared to the group that expired (0%). However, it is important to note that this

Table 1. Demographic Characteristics of the study participants:

Parameters		**No. (%)**
	Male	16 (47.06)
Gender	Female	18 (52.94)
Age	0-3 years	16 (47.06)
	> 3-6 years	9 (26.47)
	> 6-9 years	3 (8.82)
	> 9 years	6 (17.65)
Socio-economic classification	I	0 (0)
	II	5 (14.71)
	III	20 (58.82)
	IV	9 (26.47)
Symptoms	Fever	32 (94.12)
	Convulsion	25 (73.53)
	Vomiting	19 (55.88)
	Altered Sensorium	16 (47.06)
	Anorexia	14 (41.18)
	Cough	11 (32.35)
	Weakness	11 (32.35)
	Headache	5 (14.71)
	Weight Loss	3 (8.82)
Contact history	Present	6 (17.65)
	Absent	28 (82.35)
BCG Vaccination	Vaccinated	19 (73.08)
	Survived	
	Expired	7 (26.92)
	Unvaccinated	5 (6 2 . 5)
	Survived	
	Expired	3 (37.5)

Table 2. The age distribution, stages of disease and Mortality

		Expired		
Age	Stage-I	Stage-II	Stage-III	total
0-3 years	0	2	0	2
> 3- 6 years	0	2	2	4
> 6-9 years	0	0	0	0
> 9 years	0	4	0	4
Total	0	8	2	10

Table 3. Signs of Raised Intracranial Tension on admission and its relation to mortality.

	S/O Raised Intracranial Tension		
	Present	Absent	Total
Expired	7	3	10
Survived	7	17	24
Total	14	20	34

Table 4. Comparison of CSF Findings in Expired and Survived Group

CSF Findings		Expired group	Survived group
Protein (mg dL)	< 40	0	3
	40-100	0	2
	> 100	10	19
Sugar (mg dL)	< 20	1	0
	20 - 50	6	16
	> 50	3	8
Total Cells	< 10	0	11
(per Cu mm)	10 - 50	8	2
	> 50	2	9
Lymphocytes of	< 50	0	2
Total Cells	> 50	10	24

Table 5. CT Head Abnormalities in Neurotuberculosis

Abnormality On CT Head	No. of Patients (%)	S/O Increased Intracranial Tension (%)
Meningeal Enhancement	11 (52.38)	5 (35.71)
Hydrocephalus	16 (76.19)	9 (64.29)
Periventricular Oedema	9 (42.86)	3 (21.43)
Infarcts	5 (23.81)	3 (21.43)
Tuberculoma	3 (14.29)	1 (7.14)

Table 6. Role of CT scan / MRI in Diagnosis Improving Diagnostic Accuracy of TBM/Neurotuberculosis.

Diagnosis Evident without CT scan	32
Diagnosis Evident after CT scan	2
Total	34

difference did not reach statistical significance. A total of 7 out of 10 patients who experienced mortality exhibited indications of elevated intracranial tension (ICT). In contrast, among those without signs of increased intracranial tension the mortality rate was 3 out of 10. The reasons for mortality in this latter group were attributed to other morbidity factors, such as pleural effusion, hyponatremia and aspiration pneumonia. Consequently the manifestation of raised ICT features unequivocally correlated with adverse outcomes, as outlined in Table 3.

Chest X-ray abnormalities were identified in 12 out of 34 patients (35%), indicating its utility in investigating extracranial tuberculosis in cases of Neurotuberculosis. Among these, nine patients exhibited consolidation, while miliary tuberculosis, hilar adenopathy and pleural effusion were relatively infrequent.

In our investigation, 29 out of 34 analyzed cerebrospinal fluid (CSF) samples, constituting 79%, demonstrated a protein content equal to or exceeding 100 mg dL. Conversely, a smaller proportion, 21%, exhibited a protein content of 100 mg dL or less. Among the total 34 samples, 23 (68%) displayed glucose content below 50 mg dL, with 14% falling within the range of 0-100 mg dL. Only 6 out of 34 samples indicated CSF glucose levels surpassing 100 mg dL, indicating a limited sensitivity of CSF glucose in the diagnosis of tuberculous meningitis (TBM). Regarding cell count, 2 out of 34 patients exhibited pleocytosis, while 11 had no pleocytosis. Among those with pleocytosis, 10 patients had a cell count ranging from 10 to 50, 7 had a count between 50 and 100 and 6 had a count exceeding 100 cells. Furthermore, 32 out of 34 (94%) CSF samples displayed lymphocytosis, with lymphocytes constituting more than 50% of the total cell count. Only 2 out of 34 samples (6%) exhibited lymphocytes as less than 50% of the total cells. Thus, lymphocytic cellular predominance emerged as a prevalent and crucial feature of TBM. Analysis of CSF parameters revealed a higher CSF protein level in the entire expired group (100%) compared to the survived group (79%). Similarly, a higher percentage of CSF lymphocytes relative to total cells was observed in the expired group (100%) compared to the survived group (92%) and this difference was deemed statistically significant, as detailed in Table 4.

A total of 21 CT head scans and 3 MRIs were conducted among the 34 patients enrolled in the study. The interpretation of all CT head scans was performed by the same radiologist at SSG Hospital, Vadodara. Among the CT head scans, one patient exhibited entirely normal results, while in 10 patients, CT head imaging was not feasible due to the compromised general condition of the patients. Hydrocephalus emerged as the predominant finding in CT head scans, with 16 out of 21 cases (76.19%) displaying this condition. Other notable findings included meningeal enhancement (52.38%), periventricular ooze (42.8%), infarction (23.81%) and tuberculoma (14.29%).

Among the 24 patients clinically suspected of having raised intracranial tension (ICT), 9 displayed mild hydrocephalus and 8 exhibited moderate hydrocephalus. Thus, it was observed that all patients with clinical indications of raised ICT presented with hydrocephalus. In contrast, among the 15 patients with no signs of raised ICT, only 7 had hydrocephalus, mostly of a moderate degree. Consequently, it can be safely concluded that hydrocephalus consistently accompanies patients with clinical signs of raised ICT. However, predicting the severity of hydrocephalus based on clinical indications of raised ICT, as opposed to neuroimaging, proved challenging, as both groups primarily exhibited moderate hydrocephalus. In the cohort of patients with hydrocephalus on CT scan, 3 out of 16 died, compared to 1 death in the group without hydrocephalus on neuroimaging. Although the sample size was limited the mortality rates were comparable.

The study findings indicated that patients with stage II and III disease tended to present with moderate or severe hydrocephalus, as reported by the radiologist. Notably the single case in stage I disease exhibited mild hydrocephalus. While there appeared to be some correlation between the disease stage and the degree of hydrocephalus, this association did not achieve statistical significance. The basal ganglia was the most common site of infarction (28%), followed by the cerebral hemisphere (10%) and thalamus (5%). The presented table delineates instances wherein the diagnosis of Tuberculous Meningitis/Neurotuberculosis (TBME/NTB) was ascertainable prior to CT/MRI examinations, relying on clinical observations supported by cerebrospinal fluid (CSF) analysis, X-ray results and tuberculin tests. Nonetheless, in two cases, the routine investigations failed to establish a definitive diagnosis. Notably, distinctive CT findings strongly indicated the presence of tuberculoma in these instances. Consequently, CT/MRI procedures were deemed necessary for confirmation of the diagnosis in only two out of the total 34 cases.

DISCUSSION

In the current investigation, there were 18 female and 16 male participants, resulting in a male to female ratio of 0.8:1. This contrasts with several previous studies indicating a male predominance, with a male to female ratio ranging from 1.3:1 to 1.5:1, comprising 59% males and 41% females[13-16]. Notably, a study by M. Gelabert and Castro-Gago and M. Sobri revealed that a substantial majority of patients (74%) were below 5 years of age. Thilothammal reported that 30% of children were under 2 years of age, while 40% were

between 2 and 5 years. Similarly, a study in the Philippines found that 77% of children with Tuberculous Meningitis (TBM) were under 5 years of age. These findings align with the demographic distribution observed in our study[13-16].

Within our investigation, a predominant proportion of the patients fell into socioeconomic classes III and IV, a finding consistent with studies conducted by Thilothammal *et al*.[16] and Rashmikumar *et al*.[17]. The prevalent clinical manifestations in our study included fever as the most common complaint, followed by convulsions. These observations align with the findings reported by Lee *et al*. in an 11-year study, where fever was present in 88%, vomiting in 57%, cough/cold in 3%, anorexia in 29% and headache in 28%, demonstrating concordance with our study[15]. Similarly, a study in Pakistan showed constitutional symptoms in 80% of cases and headache in 86%, further corroborating our results[18]. It is noteworthy that our study group primarily comprised patients under the age of 3 years, potentially explaining the lower prominence of headache as a symptom in our findings.

Among the total of 34 patients, 6 reported having contact with relatives diagnosed with tuberculosis. This observation aligns with the findings of prior studies, including those conducted by M. Gelaber *et al*. (where 14 out of 26 children had contact with relatives with tuberculosis) and Zafer Iqbal *et al*. (indicating 7 out of 30 children had a history of contact with relatives with tuberculosis)[13,18]. Thilothammal identified a family history of tuberculosis in 33% of cases and a history of Kochs in the neighborhood in 6%[16]. Furthermore, a study in the Philippines reported a family history of tuberculosis in 69% of cases[15].

The current investigation reveals no statistically significant difference in the incidence of Neurotuberculosis between vaccinated and unvaccinated patients, a finding consistent with the observations made by Mukesh *et al*.[19]. Conversely, a study conducted by Col R. Gupta et al. reported a statistical significance between BCG non-vaccinated cases and the occurrence of Neurotuberculosis[20]. According to the Indian Academy of Pediatrics (IAP) guidebook on vaccination the Bacillus Calmette-Guérin (BCG) vaccine demonstrates an efficacy ranging from 50% to 80% for the prevention of miliary tuberculosis and the meningeal form of the disease[21].

In the current investigation, a higher mortality rate was observed in disease stage II among individuals aged less than 6 years, a finding consistent with studies conducted by Mukesh *et al*. and Thwaites *et al*.[19,22]. Conversely, studies by Zafar *et al*. and DPE Kingsley *et al*. reported a higher mortality rate in stage III[18, 12]. Among the patients who expired in our study, 7 out of 10 exhibited signs of raised intracranial tension (ICT), aligning with findings from a study by Thwaites *et al*. which indicated that evidence of raised intracranial tension was associated with a poor prognosis[22]. The cerebrospinal fluid (CSF) findings for both surviving and deceased patients are delineated in Table 4. Thilothammal reported pleocytosis in 85% of cases, with only 50% exhibiting lymphocytic predominance. Elevated CSF protein levels were observed in 91% of patients, and while there was an association between CSF protein and mortality, it did not reach statistical significance[16].

A study in the Philippines indicated that only 13% of cases had CSF protein levels below 45 mg%, while 65% exhibited levels above 100 mg%. Additionally, sugar levels were lower than 50% of blood sugar in 80% of cases and 45% had cell counts ranging between 60 and 500 cells/cu mm. Half of the cases had cell counts less than 60/cu mm[15]. Humphries *et al*. [24] documented a mean cerebrospinal fluid (CSF) protein level of 258 mg dL. There was no statistically significant difference in CSF protein levels observed among the three clinical stages of tuberculous meningitis (TBM). Likewise, no significant disparity was noted in CSF glucose levels across the three TBM stages. The mean cell count was recorded as 260/cu mm, with no significant difference in the total cells per cubic millimeter of CSF observed among the three stages. Lymphocyte predominance was evident in 83% of cases.

In a study conducted by Mukesh Agrawal[19], no significant distinctions were found in the protein or sugar content of CSF between individuals who succumbed to the condition and those who recovered. However the prognosis exhibited a substantial deterioration with an increase in the cell count. In the present study, hydrocephalus emerged as the predominant finding on CT head scans, with 16 out of 21 cases (76.19%) exhibiting this condition. This was followed by meningeal enhancement (52.38%), periventricular ooze (42.8%), infarction (23.81%), and tuberculoma (14.29%). These findings, indicative of Tuberculous Meningitis (TBM), align with the observations of various researchers, including DPE Kingsley, Garg and Satya Gupta *et al*.[20,23,25].

In S. Bhargava's study[26], hydrocephalus was reported in 83% of cases and infarcts were identified in 28% of cases. Bullock's study[27] noted hydrocephalus in 76% of cases, meningeal enhancement in 64% and basal lucency in 32%. Additionally, in a study conducted by Kumar *et al*. hydrocephalus was observed in 87% of cases, with infarcts in 28% and the basal ganglia being the most commonly affected region [28].

CONCLUSION

The diagnosis of Tuberculous Meningitis (TBM) primarily relied on clinical assessments, routine laboratory findings, tuberculin tests and chest X-rays.

The incorporation of neuroradiological imaging techniques such as CT scans and MRI only marginally enhanced diagnostic accuracy, as observed in 2 out of 34 cases in the present study. Decisions regarding the initiation of Anti-Tuberculosis Treatment (AKT) were primarily guided by the diagnosis of TBM/Neurotuberculosis (NTB) and the inclusion of CT scans/MRI only resulted in marginal improvements in management decisions.

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