ACCURACY OF ESTABLISHED CRANIAL CT SCAN FINDINGS IN THE DIAGNOSIS OF CRANIAL TUBERCULOSIS

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ABSTRACT

Objective. Diagnosis of Central Nervous System tuberculosis (CNS TB) can be confirmed with clinical, laboratory parameters and therapeutic response to treatment. Because of the nonspecificity of the clinical findings and the invasive nature of CSF analysis in the pediatric patient, neuroimaging provides a non-invasive means to improve diagnostic accuracy.

Methodology. This is a blinded, retrospective review of cranial CT scans of 100 patients (<17 yrs old) by three radiologists. Nine disease groups were evaluated. Specific imaging characteristics include cisternal hyperdensity, hydrocephalus, meningeal enhancement, edema, calcification, and mass. Patients with normal cranial CT scan were utilized as control. Clinical information, CSF analysis, and response to therapy were used to establish definitive diagnosis. Statistical Package for Social Sciences (SPSS Version 16) was used to analyze the data.

Results. Hydrocephalus (80%) with edema, abnormal meningeal enhancement (70%), and infarction (63%) are the most sensitive predictors of CNS-TB. Calcification is not a strong predictor. Basal cistern hyperdensity on noncontrast study is the most specific predictor at 100%. The radiologists were highly accurate differentiating normal from abnormal scans. Specific CT scan findings are highly accurate for CNS-TB diagnosis.

Conclusions/Recommendations. In this study, the radiologists were highly accurate in the diagnosis of CNS-TB. The presence of basal cistern hyperdensity on the non-contrast enhanced study is the most specific finding in the diagnosis of CNS-TB. Hydrocephalus, edema and infarctions could also be noted. Upon administration of contrast, basal cistern enhancement also increases sensitivity of the diagnosis.

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Tuberculosis continues to be an important cause of hospital admissions, deaths and neurologic disability. It is the seventh leading cause of death and disability worldwide. The incidence of CNS TB is related to the prevalence of TB in the community. In developing countries, it is the most common type of chronic CNS infection. About 1.4 million cases of TB occur annually in the developing world. Forty thousand TB-related deaths occur in children younger than 15 years. One out of every 300 untreated primary TB infection is complicated by tuberculous meningitis. Diagnosis of CNS TB is difficult to make based on clinical findings alone. Diagnosis of CNS TB can be confirmed with clinical, laboratory parameters and therapeutic response to treatment. Because of the nonspecificity of the clinical findings and the invasive nature of CSF analysis in the pediatric patient, neuroimaging provides a noninvasive means to improve diagnostic accuracy. However, diagnostic confusion often exists between tuberculous meningitis and other meningoencephalitides. The role of CT in the diagnosis of intracranial tuberculosis has not been well established. There have been a few papers written describing some CT features of intracranial tuberculosis. The motivation for this study is to describe, evaluate and assess the accuracy of these different CT imaging findings in the diagnosis of CNS TB.

METHODOLOGY

We performed a 4-year retrospective review (2004-2008) of cranial CT scans of children who presented clinically with seizures and suspected to have an intracranial infection. The scans were reviewed by three different radiologists with varying levels of expertise (Radiologist A is a senior pediatric radiologist, radiologist B is a junior pediatric radiologist and radiologist C is a senior radiology resident). All radiologists were blinded with the clinical information of all subjects. A total of 105 patients were included. All patients underwent a non-contrast and contrast-enhanced cranial CT scan. The seven established specific CT imaging characteristics of CNS tuberculosis that were evaluated include cisternal hyperdensity (predictor 1), hydrocephalus (predictor 2), meningeal enhancement (predictor 3), infarction (predictor 4), edema (predictor 5), calcification (predictor 6), and mass (predictor 7). A questionnaire [Figure 1] was filled-up by each

radiologist for each subject. Patients with normal cranial CT scan were utilized as control. Clinical information, CSF analysis, and response to therapy were used to establish the definitive diagnosis. Statistical Package for Social Sciences (SPSS Version 16) was used to analyze the data.

RESULTS

Of the 105 patients, 38 were proven to have CNS tuberculosis, 36 were normal, 5 had bacterial meningitis, another 5 had viral meningitis, 15 had other infections and 6 had malignancy.

Statistical Analysis – Radiologist A

Table 1. CT Predictors among TB Meningitis and Non-TB Meningitis Patients

Predictor	TBM N=38	Non-TBM N=67	P Value
1	*17*	*0*	*.0001*
2	*35*	*12*	*.0001*
3	*24*	*8*	*.005*
4	*22*	*9*	*.034*
5	*28*	*12*	*.011*
6	12	10	.463
7	8	9	.231

Table 2. CT predictors for each group including sensitivities, specificities, positive predictive values (PPV), negative predictive value (NPV) and likelihood ratios for diagnosing TB Meningitis

Predictor	TBM N=38	Non-TBM N=67	Sensitivity	Specificity	PPV	NPV	Likelihood Ratio
1	17	0	45	*100*	100	76	N/A a
2	35	12	*92*	82	74	95	5.14
3	24	8	*63*	*88*	75	81	5.28
4	22	9	58	*87*	71	78	4.3
5	28	12	*74*	82	70	85	4.11
6	12	10	32	85	55	69	2.11
7	8	9	21	*87*	47	66	1.56

[a]*N/A = Not applicable*

Table 3. Sensitivities, specificities, positive predictive values (PPV), negative predictive value (NPV) and likelihood ratios at various levels of predictors in diagnosing TB Meningitis

Predictor	TBM N=38	Non-TBM N=67	Sensitivity	Specificity	PPV	NPV	Likelihood Ratio
One or more predictors	38	28	100	43	58	100	2.39
Two or more predictors	36	21	95	69	63	96	3.02
Three or more predictors	28	13	74	81	68	84	3.79

Statistical Analysis – Radiologist B

Table 1. CT Predictors among TB Meningitis and Non-TB Meningitis Patients

Predictor	TBM N=38	Non-TBM N=67	P Value
1	*11*	*0*	*.001*
2	*33*	*12*	*.0001*
3	*25*	*9*	*.005*
4	*25*	*12*	*.040*
5	*29*	*12*	*.004*
6	12	11	.388
7	9	9	.345

Table 2. CT predictors for each group including sensitivities, specificities, positive predictive values (PPV), negative predictive value (NPV) and likelihood ratios for diagnosing TB Meningitis

Predictor	TBM N=38	Non-TBM N=67	Sensitivity	Specificity	PPV	NPV	Likelihood Ratio
1	11	0	29	*100*	100	71	N/A a
2	33	12	*87*	82	73	92	4.84
3	25	9	*66*	*87*	74	82	4.89
4	25	12	*66*	82	68	81	3.67
5	29	12	*76*	*82*	71	86	4.26
6	12	11	32	*84*	52	68	1.92
7	9	9	24	*87*	50	67	1.76

Table 3. Sensitivities, specificities, positive predictive values (PPV), negative predictive value (NPV) and likelihood ratios at various levels of predictors in diagnosing TB Meningitis

Predictor	TBM N=38	Non-TBM N=67	Sensitivity	Specificity	PPV	NPV	Likelihood Ratio
One or more predictors	38	27	100	60	58	100	2.48
Two or more predictors	36	19	95	72	65	96	3.34
Three or more predictors	28	11	74	84	72	85	4.48

Statistical Analysis – Radiologist C

Table 1. CT Predictors among TB Meningitis and Non-TB Meningitis Patients

Predictor	TBM N=38	Non-TBM N=67	P Value
1	*17*	*0*	*.0001*
2	*35*	*11*	*.0001*
3	*34*	*8*	*.0001*
4	*36*	*16*	*.0001*
5	*28*	*12*	*.003*
6	14	10	.444
7	10	9	.506

Table 2. CT predictors for each group including sensitivities, specificities, positive predictive values (PPV), negative predictive value (NPV) and likelihood ratios for diagnosing TB Meningitis

Predictor	TBM N=38	Non-TBM N=67	Sensitivity	Specificity	PPV	NPV	Likelihood Ratio
1	17	0	45	*100*	100	76	N/A a
2	35	11	*92*	84	76	95	5.61
3	34	8	*89*	*88*	81	94	7.49
4	36	16	*95*	76	69	96	3.96
5	28	12	74	82	70	85	4.11
6	14	10	37	85	58	70	2.46
7	10	9	26	*87*	53	67	1.95

[a]*N/A = Not applicable*

Table 3. Sensitivities, specificities, positive predictive values (PPV), negative predictive value (NPV) and likelihood ratios at various levels of predictors in diagnosing TB Meningitis

Predictor	TBM N=38	Non-TBM N=67	Sensitivity	Specificity	PPV	NPV	Likelihood Ratio
One or more predictors	38	30	100	55	56	100	2.23
Two or more predictors	38	23	100	66	62	100	2.91
Three or more predictors	36	10	95	85	78	97	6.34

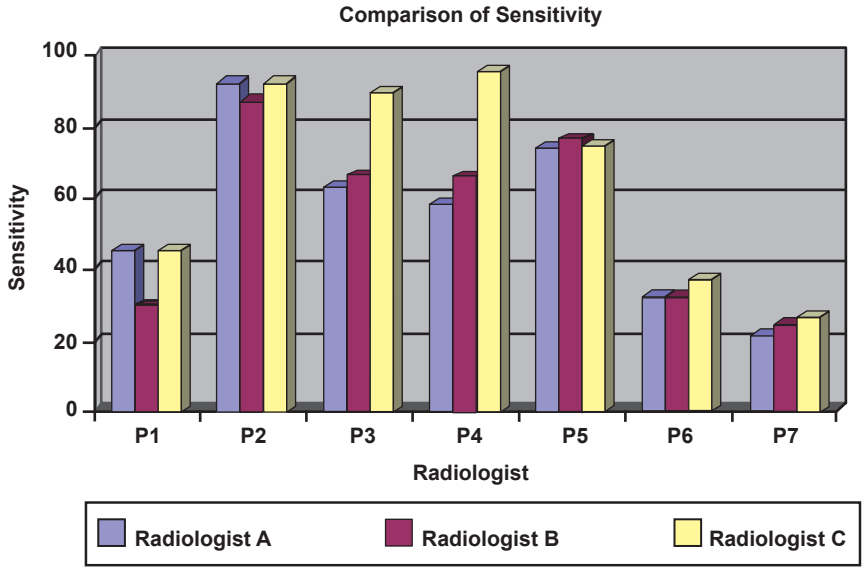

Figure 1. Comparison of the sensitivity of the different CT predictors.

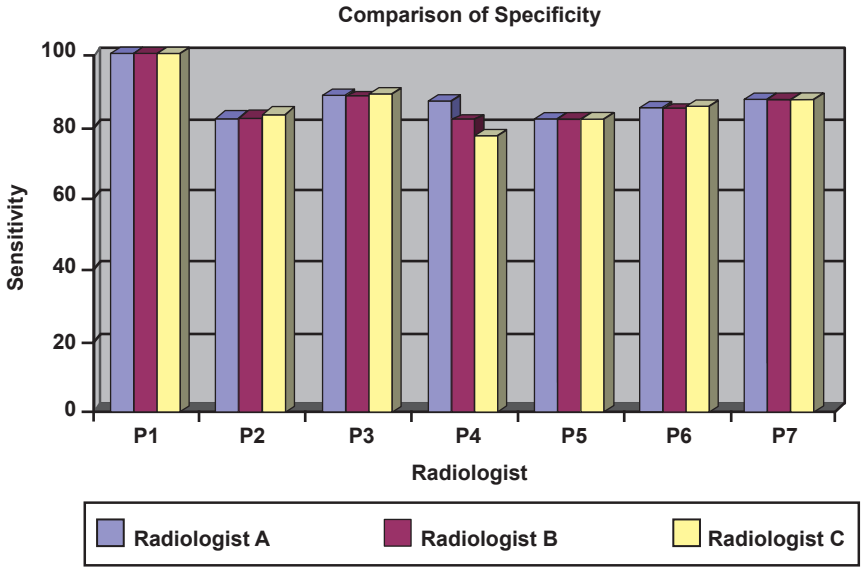

Figure 2. Comparison of the specificity of the different CT predictors

Figure 1. Standard Questionnaire. Each Radiologist fills up a standard questionnaire for each patient included in the study.

Figure 2. Basal cistern enhancement in a patient with TB meningitis. Axial CT scan image following intravenous administration of contrast demonstrates significant enhancement along the basal cisterns (arrows).

Figure 3. Infarction in a child diagnosed with TB meningitis. Axial CT scan image demonstrates low attenuation (low density) in the region of the left basal ganglia consistent with infarction (arrows).

Figure 4. Obstructive hydrocephalus and infarction in a child with CNS TB. Axial CT scan image demonstrates significant dilatation of the lateral ventricles (asterisks) compatible with hydrocephalus. Areas of low density similar to the cerebrospinal fluid is seen along the left periventricular region (arrows) representing sequelae of infarction.

Figure 5. Edema with hydrocephalus and punctuate calcification. Axial CT scan image showing dilated lateral ventricles compatible with hydrocephalus (asterisks). There is low density area on the left frontal lobe compatible with edema (straight arrows). Punctate area of high density in the left frontal lobe adjacent to the ventricle is compatible with focal calcification (open arrow).

Figure 6. Intracranial mass in a child diagnosed with CNS TB. Axial CT scan image without contrast (Fig 6A) and following intravenous contrast administration (Fig 6B) shows a large, ovoid brain lesion with thick irregular peripheral enhancement (asterisk) at the left frontotemporal lobe with moderate perilesional edema (arrows).

Figure 7. Abnormal cisternal increase intensity in a child diagnosed with TB meningitis. Fig 7 A is an axial non-contrast CT scan image showing increased attenuation/density at the perimesencephalic and basilar cisterns (arroes) on the non-contrast images. Following intravenous administration of contrast (Figure 7B), abnormal leptomeningeal enhancement (arrows) was noted along the cisterns commonly seen in TB meningitis.

Figure 8. Abnormal cisternal increase density (arrows) in a patient with TB meningitis is seen along the basal cisterns on this non-contrast CT scan image.

Data Analysis

Predictors for presence or absence of TB meningitis was compared by univariate analysis, x^2 test or Fischer exact test where applicable using SPSS (Statistical Package for Social Sciences) version 16.0. Data analyses were 2-tailed at 95% confidence interval.

The CT predictors were compared with the gold standard diagnosis (positive CSF & clinical) in a two by two table to calculate its sensitivity, specificity, and the likelihood ratios for various predictors and their combinations.

DISCUSSION

Many of the symptoms, signs, and sequelae of tuberculous meningitis (TBM) are the result of an immunologically directed inflammatory reaction to the infection. The development of TBM is a 2-step process. It starts with the Mycobacterium tuberculosis bacilli entering the host by droplet inhalation, the initial point of infection being the alveolar macrophages. Localized infection intensifies within the lungs, with spread to the regional lymph nodes to produce the primary complex. During this period, a short but significant bacteremia is present that could lead to the tubercle bacilli dissemination to other organs in the body.

In persons who develop CNS TB, the bacilli seed to the meninges or brain parenchyma, with resultant formation of small subpial or subependymal foci of metastatic caseous lesions. These are termed Rich foci. Tuberculous pneumonia could develop with heavier and more prolonged tuberculous bacteremia. Dissemination to the CNS is more likely, particularly if miliary TB develops.

The second step in the development of CNS TB is enlargement of a Rich focus until it breaks into the subarachnoid space. The location of the expanding tubercle (ie, Rich focus) determines the type of CNS involvement. Tubercles rupturing into the subarachnoid space cause meningitis while those deeper in the brain or spinal cord parenchyma cause tuberculomas or abscesses. While an abscess or hematoma can rupture into the ventricle, a Rich focus does not.

A thick gelatinous exudate penetrates the cortical or meningeal blood vessels, producing inflammation, obstruction, or infarction. Basal meningitis accounts for the frequent dysfunction of cranial nerves III, VI, and VII, eventually leading to obstructive hydrocephalus from obstruction of basilar cisterns. Subsequent neurological pathology is produced by 3 general processes: adhesion formation, obliterative vasculitis, and encephalitis or myelitis.

Tuberculomas are conglomerate caseous foci within the substance of the brain. Centrally located, active lesions may reach considerable size without producing meningitis. Under conditions of poor host resistance, this process may result in focal areas of cerebritis or frank abscess formation, but the usual course is coalescence of caseous foci and fibrous encapsulation (ie, tuberculoma). Paradoxical development or enlargement of tuberculomas during antituberculous chemotherapy has also been re-

ported; it possibly has an immunological basis.

In the tuberculous process, the spinal meninges may be involved, owing to the spread of infection from intracranial meningitis, primary spinal meningitis in isolation as a result of a tuberculous focus on the surface of the cord rupturing into the subarachnoid space, or transdural extension of infection from caries of the spine.

Pathologically, a gross granulomatous exudate fills the subarachnoid space and extends over several segments. Vasculitis involving arteries and veins occurs, sometimes resulting in ischemic spinal cord infarction.

Presently, more than 2 billion (2000 million) people in the world are infected with TB (ie, one third of the world's population), of which approximately 10% will develop clinical disease. The incidence of CNS TB is related to the prevalence of TB in the community, and it is still the most common type of chronic CNS infection in developing countries. Despite great advances in immunology, microbiology, and drug development, TB remains among the great public health challenges. Poverty; lack of functioning public health infrastructure; lack of funding to support basic research aimed at developing new drugs, diagnostics, and vaccines; and the co-epidemic of HIV continue to fuel the ongoing epidemic of TB.

Although pulmonary TB tends to be the most common form of TB, the highest morbidity and mortality occurs in TBM. Tuberculous meningitis is a serious illness, which if not diagnosed and managed early, could lead to serious neurologic sequelae. Mortality rate has been estimated to vary from 15% to 32%. This makes it the leading cause of infectious death worldwide.

Early diagnosis of TBM continues to pose a challenge. Delay in diagnosis and correct treatment is directly related to poor outcome. Clinical presentation is nonspecific, overlapping with a lot of other disease entities. Definitive diagnosis is established by demonstration of mycobacteria in the cerebrospinal fluid, by direct staining or culture. But aside from being an invasive procedure, this is time consuming and seldom positive. Recognizing this problem of diagnosis, newer tests have been developed to differentiate TBM from other meningitides, such as polymerase chain reaction, enzyme linked immunosorbent assay, bromide partition test, etc. But the sensitivity of these tests is still under study and unlikely to be readily available where they are really needed. Thus, neuroimaging, CT scan in particular, will really be helpful as it can differentiate various patterns of CNS infections and is readily available.

The described classic finding of marked basal cistern enhancement in TBM [Figure 2] in different literature is again proven in this paper. Its incidence greatly varies in the reported literature being 11% to 93%. In our paper, its sensitivity is valued at 73% while the specificity is 88%. The occurrence of abnormal basal cistern enhancement may be due to meningeal inflammation, an enhancing gelatinous exudates and/or granulomatous tissue that completely or partially fills the basal cisterns. These exudates can extend into the Sylvian and hemispheric fissures and over the cortical surfaces of the brain.

The presence of infarction [Figure 3], which is seen most commonly in the region of the basal ganglia as it is supplied by end arteries, is due to the inflammatory exudates infiltrating the blood vessels running through the involved CSF spaces causing a panarteritis. Its sensitivity in this study is valued at 75%. Specificity is 82%.

Consequently, the flow of CSF will be adversely affected resulting in obstructive hydrocephalus [Figure 4], most commonly of the communicating type because obstruction at the level of the arachnoid villi usually occurs. Sensitivity of this imaging predictor is computed at 93% while specificity is 83%.

Cerebral edema is to be expected in the course of an ongoing inflammation. This could also represent transependymal seepage of cerebrospinal fluid from the ventricles into the adjacent brain parenchyma as a result of hydrocephalus. On CT imaging, this manifests as decreased attenuation particularly at the periventricular region if there is active ventricular obstruction [Figure 5]. Its sensitivity is 75% and specificity is 82%.

The presence of parenchymal calcification [Figure 5] as well as mass [Figure 6] although highly specific for CNS TB with computed values at 84% and 86% respectively, are not very good predictors as their sensitivity is computed at 32% and 22% respectively.

A relatively recent described CT imaging feature is the increased density appearance along the basilar cistern on the non-contrast examination [Figure 7]. This may be attributed to the presence of purulent exudates in these CSF spaces. In our study, its sensitivity is very high at 100%. However, sensitivity is low at 40%. As this is a relatively new described imaging characteristic of CNS TB, not all radiologists may be that cognizant and sensitive in recognizing it. It is therefore very important to consciously look at subtle density changes at the region of the basal cistern if CNS TB is a consideration.

In summary, hydrocephalus (93%), abnormal meningeal enhancement (73%), and infarction (75%) are the most sensitive predictors of CNS-TB. Calcification is not a strong predictor. Basal cistern hyperdensity on noncontrast study is the most specific predictor at 100%. The radiologists were highly accurate differentiating normal from abnormal scans. Specific CT scan findings are highly accurate for CNS-TB diagnosis.

CONCLUSION/RECOMMENDATION

Several CT imaging parameters have been described. In this study, the radiologists were highly accurate in the diagnosis of CNS-TB. The presence of basal cistern hyperdensity on the non-contrast enhanced study is the most specific finding in the diagnosis of CNS-TB. Hydrocephalus, edema and infarctions could also be noted. Upon administration of contrast, basal cistern enhancement also increases sensitivity of the diagnosis. It is therefore recommended that radiologists working in regions with a high incidence of TBM be trained and very familiar with and recognize these CT features. This will significantly further increase the diagnostic accuracy of CT in TBM.

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