DIAGNOSTIC ACCURACY OF CONTRAST ENHANCED T2 FLAIR IN DIAGNOSING INFECTIVE MENINGITIS CONSIDERING CSF ANALYSIS AS GOLD STANDARD

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ABSTRACT

Background: Meningitis is the inflammation of meninges giving particular symptoms like fever, headache, neck rigidity and altered sensorium.

Objective: To determine diagnostic accuracy of contrast enhanced T2 FLAIR in diagnosing infective meningitis considering CSF analysis as gold standard.

Methods: A prospective study of 101 patients with clinical suspicion of meningitis, referred to the radiology department of Mayo Hospital Lahore for MRI examination was done. Patients with reduced renal function, claustrophobia and metallic implants were excluded from the study. The CE MRI brain including postcontrast T1WI and FLAIR sequences was performed at 1.5 T machine. The images then evaluated by the competent experienced radiologists. Cerebrospinal fluid (CSF) analysis of the patients was done through lumbar puncture and considered to be the "gold standard" against which comparison of MRI findings was done. Data analysis was done by using SPSS 23.

Results: Sensitivity and specificity of CE T2 FLAIR MRI in detecting infective meningitis was 95.08% (CI-95%: 86.51-98.31) and 82.5% (CI-95%: 68.05, 91.25). The positive predictive value and negative predictive value was 89.23% (CI-95%: 79.4, 94.68) and 91.67% (CI-95%: 78.17, 97.13) respectively. Diagnostic accuracy was 90.1% respectively.

Conclusion: Results of this study showed higher sensitivity and specificity for contrast enhanced T2 FLAIR in diagnosing infective meningitis. So, addition of CE T2 FLAIR in MRI brain protocols can be helpful in early screening and diagnosis of meningeal infections.

Key words: Meningitis, CSF, Diagnostic accuracy, Magnetic Resonance Imaging, Contrast Enhanced FLAIR

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INTRODUCTION

Meningitis is the inflammation of meninges giving particular symptoms like fever, headache, neck rigidity and altered sensorium.[1] The prevalence of meningitis in our region is approximately 15%.[2] Meningitis has high morbidity and mortality if undiagnosed, diagnosed late

or not properly managed. In hospitalized patients the tuberculous meningitis has been reported to cause about 42% mortalities.[3] In acute bacterial meningitis, death can occur upon delayed management and administration of antibiotics. The risk of death increases 8.4 folds with delay of in administration of antibiotics as soon as 4 to 6 hours, that is particularly significant in children and elderly.[4] Neuroimaging is very important in early and reliable diagnosis of infective meningitis. CE CT scan may yield abnormal meningeal enhancement, sulcal effacement, periventricular enhancement (especially in tuberculous meningitis) and non-communicating hydrocephalus. CE T1WI scan may show hypointense T1 signals from sulci, abnormal meningeal enhancement, cytotoxic cerebral edema, tuberculomas and venous infarction.[1] Role of MR imaging is very conspicuous for the diagnosis of meningitis as it is unaffected from bony artifacts and has better soft tissue details, yet gold standard is CSF analysis through lumbar puncture. Abnormal meningeal enhancement is a primal imaging finding that can reliably elicit meningitis which is thin and linear in bacterial & viral meningitides while thick and nodular in fungal, tubercular and neoplastic meningitides.[5,6] Contrast enhanced MR study is the investigation of choice for this and CE T1WI are regularly used but recent literature has shown CE T2 FLAIR to be most sensitive and specific sequence, hence gaining popularity.

The sensitivity and specificity of CE T1WI is 92.8% and 75% respectively while the sensitivity and specificity of CE T2 FLAIR is 97.6% and 83.8% respectively.[7] The contrast enhancement that produces on T2 FLAIR is a result of mild T1 effect elicited by long T1, resultantly the lesions showing contrast enhancement on T1WI also show contrast enhancement on T2 FLAIR sequence. T1 shortening caused by Gadolinium based contrast medium is due to T1 shortening or relativity. FLAIR sequence is found to be more sensitive to T1 shortening than T1WI at lower doses of Gadolinium and is sensitive to T2 effects at high concentration. This signifies that subtle enhancing lesions on CE T1WI show significant enhancement on CE T2 FLAIR.[8] Moreover, CE FLAIR sequence nullifies the signals from CSF and shows inconspicuous vascular enhancement resulting in more conspicuous enhancement of abnormal meninges.[9] These are its attributes that makes these sequences more sensitive for detection of abnormal meningeal enhancement.

Our study compares the diagnostic accuracy of CE T2 FLAIR in diagnosing infective meningitis. As this sequence enhances the abnormal meninges significantly and more than CE T1WI, this sequence becomes very important in early and subtle meningeal enhancement

and thereby accurate and early diagnosis of acute infectious meningitis which otherwise can be very detrimental for the patient. Its attributes of CSF signals nullification, T1 relativity and inconspicuous vascular enhancement put it heads and shoulder above any other sequence of MRI and matching in its sensitivity with CSF analysis. This study compares the both and if found sensitive enough, it can become sequence of choice in diagnosing infective meningitis, especially in the patients in which lumbar puncture is contraindicated.

METHOD
This was a comparative cross-sectional study conducted at Department of Diagnostic Radiology, Mayo Hospital, Lahore. Time duration for the study was 2 years. Sample size of 101 is calculated with confidence interval(Z) of 95%, margin of error(d) 10% along with expected prevalence of infective meningitis 15 % with MRI sensitivity of 96 % and specificity of 85.71 %, taking CSF analysis as gold standard. The formula used to calculate sample size is $n = Z^2.p.q/d^2$

Sample selection was done with the help of non-probability consecutive sampling. A predefined incision and exclusion criteria were used for sample selection. i.e. Patients with symptoms of infective meningitis including fever, neck rigidity, head ache, altered state of consciousness, fits and photophobia referred to radiology department from the department of internal medicine and neurology. Patients with positive Kernig and Brudzinski signs. Patients less than 12 years age, with impaired renal function with GFR<30 ml/min, having recurrent disease, with pacemakers, prosthetic valve, aneurysm clips, plates, any other ferromagnetic material, claustrophobia and excessively irritable & mobile patient were excluded from the study.

Cultural ethics were observed by respecting the privacy of the patient and assuring proper confidentiality of patient's data. Informed consent was taken. A total of 101 patients fulfilling the selection criteria presenting to radiology department of mayo hospital were enrolled in the study after informed consent and briefing of the study to the patients. Biodata and clinical history were taken from all the patients. Investigations were checked. All of this information was recorded through Performa. MRI brain was conducted with routine sequences from vertex to base of skull on GE healthcare, sigma voyager, 1.5 Tesla MRI machine. T1 and T2 turbo spin echo sequences were done in axial, coronal and sagittal planes along with DWI images and ADC mapping. T2 FLAIR was obtained in the axial plane, that is a heavily weighted T2 sequence with long echo time, repetition time and inversion time. Then Gadolinium based contrast medium was infused at 0.1 mmol/kg dose and

CE T1WI and CE T2 FLAIR images were obtained in axial plane after 1minute and 2.5 minutes respectively. The reporting of the scan was done under the supervision of two qualified radiologists that have a working experience of 5 to 10 years. CSF analysis of all the subjects were followed. The physical findings, biochemistry, cytology, culture, glucose levels and protein levels of CSF was analyzed by a qualified pathologist. CSF analysis report was labeled as bacterial, viral, fungal or tuberculous meningitis.

Data was entered and analyzed using SPSS 23 (Statistical package for Social Scientist Version 23). All quantitative data was presented as mean ± SD e.g. age, frequency and percentage was ascertained for qualitative variables. In this study we used uniform sources of information and efficient questionnaire to avoid bias. A two-by-two contingency table was constructed to ascertain sensitivity, specificity, positive predictive value PPV, negative predictive value NPV and diagnostic accuracy. MRI machines was optimized, standardized and checked for artefacts.

	CSF analysis		
	Positive	Negative	Total
CE T2FLAIR Positive	TP	FP	TP+FP
Negative	FN	TN	FN+TN
Total	TP+FN	FP+TN	n

True Positive (TP), False Positive (FP), False Negative (FN), True Negative (TN)
Sensitivity= TP/(TP+FN) x100
Specificity= TN/(TN+FP) x100
Positive predictive value= TP/(TP+FP) x100
Negative predictive value=TN/(TN+FN) x100

RESULTS

Mean age of patients in this study was 38.81±11.32 years. Among total patients, 56 out of 101 patients (55.4%) were male and 45 out of 101 patients (44.6%) were female. Clinical signs and symptoms showed that 71(70.3%) patients had head ache, 46(45.5%) had neck rigidity, 55(54.5%) had fever, 55(54.5%) had fits, 80(79.2%) patients had altered state of consciousness, 52(51.5%) had irritability, 53(52.5%) had focal neurological deficit and 44(43.6%) patients presented with visual disturbances. Sensitivity and specificity of CE T2 FLAIR MRI in diagnosing infective meningitis was 95.08% (CI-95%: 86.51-98.31) and 82.5% (CI-95%: 68.05, 91.25), considering CSF analysis as gold standard. Atypical meningeal enhancement was seen with no CSF evidence of meningitis in 7(17.5%) cases, while no discernable meningeal enhancement was seen in the CSF proven meningitis in 3(4.9%) cases. The positive predictive value was 89.23% (CI-95%: 79.4, 94.68) and negative predictive value 91.67% (CI-95%: 78.17, 97.13). Diagnostic accuracy was 90.1% respectively.

Table-1: Demographics and clinical presentation of patients

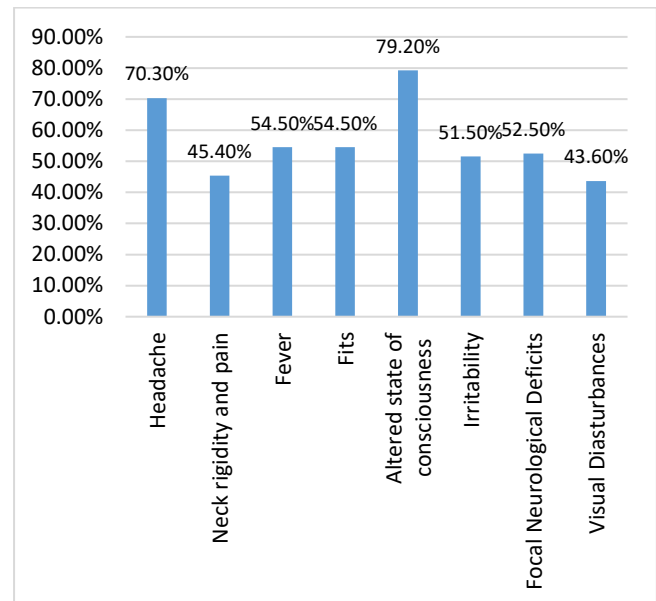| Age (Years)	38.81±11.32
Age (Range)	20-60 Years
	Frequency (%)
Gender (Male/Female)	54/45 (53.5%/46.5%)
Head Ache	71(70.3%)
Neck rigidity and Pain	46(45.5%)
Fever	55(54.5%)
Fits	55(54.5%)
Altered state of Consciousness	80(79.2%)
Irritability	52(51.5%)
Focal neurological deficit	53(52.5%)
Visual disturbances	44(43.6%)

Figure-1: Demographics and clinical presentation of patients

Table-2: Diagnostic accuracy of enhanced T2 FLAIR in diagnosing infective meningitis considering CSF analysis as gold standard

		CSF		Total
		Positive	Negative	
Contrast Enhanced T2 FLAIR	+VE	58 (95.1%) TP	7 (17.5%) FP	65
	-VE	3 (4.9%) FN	33 (82.5%) TN	36
Total		61	40	101

Sensitivity= 95.08%(86.51-98.31)
Specificity= 82.5% (68.05-91.25)
Positive Predictive value= 89.23% (79.4-94.68)
Negative predictive value= 91.67% (78.17-97.13)
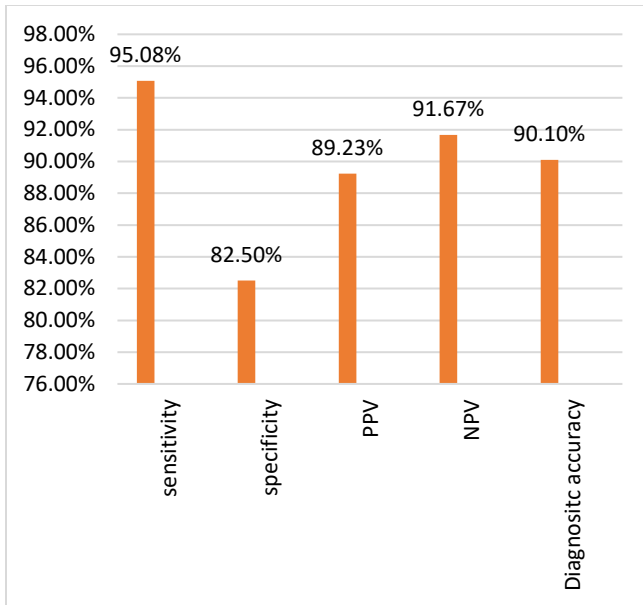**Diagnostic Accuracy=** 90.1% (82.73-94.53)

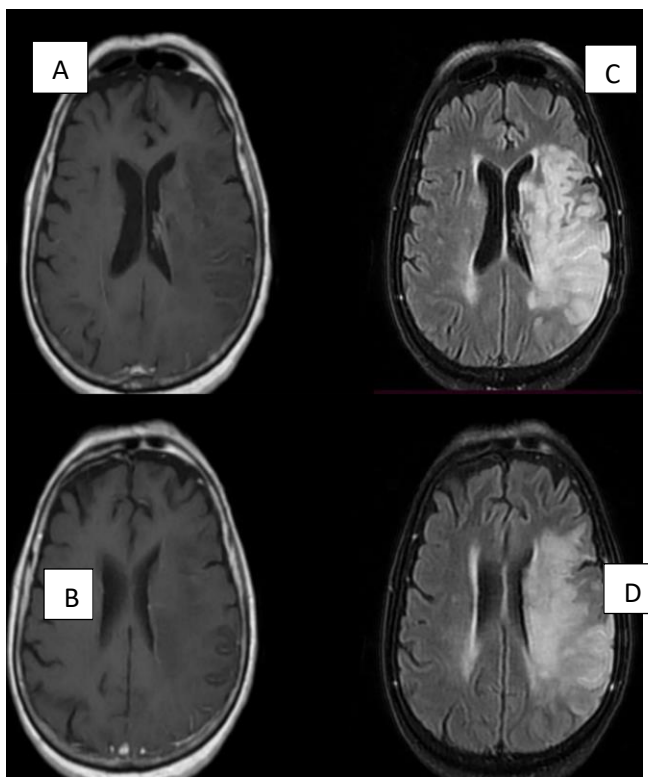**Figure 2:** Diagnostic accuracy of CE T2 FLAIR

Figure 3: A and B; Post contrast T2 FLAIR sequence axial MRI images, revealing leptomeningeal enhancement along the right frontoparietal leptomeninges. C and D; CE T1WI sequence axial MRI images showing leptomeningeal enhancement. An area of encepahlitis is seen in the right frontoparietal lobe. The patient was a known case of viral meningoencephalitis.
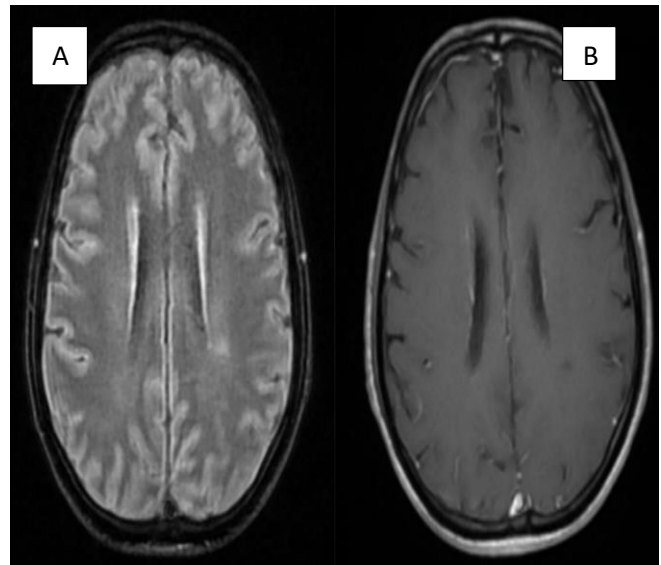

Figure 4 A; axial MRI CE T2 FLAIR image showing conspicuous leptomeningeal as well as pachymeningeal enhacement along bilateral parietal regions. B; no significant enhancement seen on the T1 post contrast image.
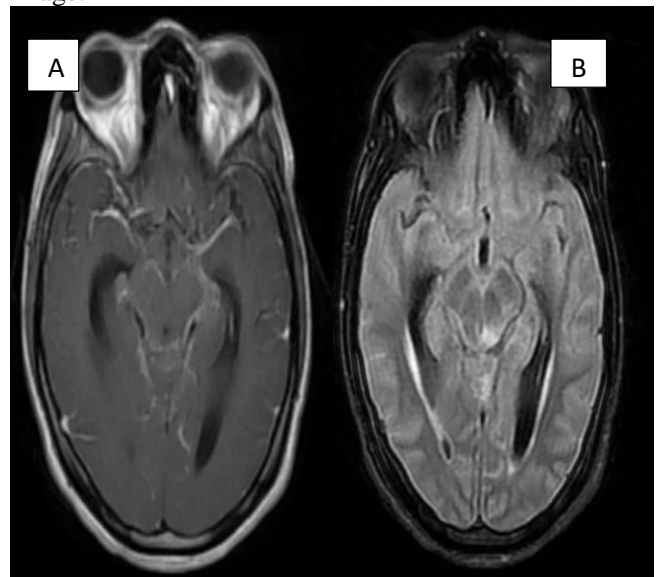

Figure 5- A; axial CE T1WI showing pachymeningeal thickening and enhacement along the midbrain while minimal letomenigeal enhancement seen along the right temporal region. B; pachymeningeal thickening and enhancement seen on CE T2 FLAIR image as well as leptomeningeal enhancememt along the right temporal lobe. A focal infarct is seen as a sequelae of the infectvie meningitis in the left tectum of midbrain.

DISCUSSION

The role of imaging is of profound value in timely diagnosis of meningitis and its complications and is made possible through evolution of imaging itself,

initially by post contrast CT, then post contrast T1WI MRI and now popularity gaining CE T2 FLAIR.[10] CE CT and CE T1 MRI images are also helpful; however, their sensitivity and specificity are less compared to the CE T2 FLAIR MRI. Local literature on the importance of CE T2 FLAIR MRI for early detection of meningitis is limited till date. Moreover, according to Lumel et al., MRI sensitivity would also depend on the severity of inflammation and the etiological factors of meningitis.[11] In this study we assessed the diagnostic accuracy of CE T2 FLAIR in diagnosing infective meningitis comparing it with CSF analysis which was rendered as gold standard. Sensitivity, Specificity, PPV and NPV for contrast enhanced T2 FLAIR was 95.08%, 82.5%, 89.23% and 91.68% respectively.

In a recent study published locally done on the 173 patients, the sensitivity, specificity, PPV, and NPV of contrast enhanced for diagnosing meningitis were determined to be 91%, 85%, 87.6%, and 89.4%, respectively, and the diagnostic accuracy was determined to be 88.4%, the results of the study are in keeping with the results of our study.[12] A prospective study of 45 patients by Kamr et al. from Egypt reported 91.1% sensitivity and 100% specificity for contrast enhanced T2 FLAIR sequences in detecting meningeal abnormalities in suspected cases of meningitis. The sensitivity of the study is in keeping with that of our study however there is difference of specificity, that might be due to the short sample size of the mentioned study.[13] Nasma Wabsa in her study reported positive predictive value for contrast enhanced FLAIR MRI as 88.8% for diagnosis of meningitis that is in keeping with the PPV of our study.[14] Using contrast-enhanced FLAIR images, Riffat Mushtaq and her team in Rawalpindi made comparison of T2 FLAIR and CSF parameters for tuberculous meningitis diagnosis. According to their findings, contrast-enhanced FLAIR MRI had 96.05% sensitivity, 92.23% specificity, 94.81% PPV, 94.06% and 94.51% diagnostic accuracy respectively.[15] Results of this study regarding diagnostic accuracy of CE T2 FLAIR showed slight variation in sensitivity, specificity, PPV, NPV and diagnostic accuracy, most notable difference seen in the specificity which may be due to difference in sample size, sampling methods, population studied and difference in certain operational definitions. Vaswani et al. in their prospective study on 57 patients done in Karachi compared the difference of sensitivities of CE T1 and CE T2 FLAIR sequences. Not that sensitivity of CE T2 FLAIR was superior to CE T1 WI, but also more conspicuous meningeal enhancement seen on CE T2 FLAIR images compared to the CE T1WI. The sensitivity T2 FLAIR postcontrast sequence was 96%, specificity was 85.71%, positive predictive value

was 97.95%, and negative predictive value was 75%, the results in keeping with the results of our study.[16]

Jesrani A et al. in their study done locally on the pediatric population of 2 to 12 years age children, revealed the sensitivity of CE FLAIR to be 78% and specificity of 83.6%, while diagnostic accuracy of 81%. Their study shows relatively reduced sensitivity compared to our study likely due to population studied and difference in inclusion criterion.[17] In a study done in Europe by Parmar et al. on 24 patients, the sensitivity and specificity of CE T2 FLAIR was found to be 85%.[18] A study done by Ahmad A et al., in which not only they did qualitative accuracy but also did quantitative analysis using single pixel signal intensities (SPSI) for CE T2 FLAIR. Qualitative accuracy was 90.2%, while quantitative assessment showed conspicuous signal difference between meningeal and vascular enhancement eventually producing greater discernable signals on CE T2 FLAIR.[19]

Post-contrast FLAIR showed better accuracy compared to post-contrast T1WI, as enhancing meninges along cerebral convexities is indistinguishable from vascular enhancement on CE T1WI, resulting in lower accuracy of CE T1WI as discussed above. Better accuracy of meningeal enhancement in CE T2 FLAIR is achieved due to suppression of signals from the cortical vessels and resultant more conspicuous meningeal enhancement.[20]

Due to the life-threatening nature of meningitis and the need to save time, every sensitive diagnostic tool available to save the patient's life should be utilized. Therefore, CE T2 FLAIR sequence when used, can help physicians diagnose meningitis with high accuracy owing to the results of the studies on CE T2 FLAIR as discussed above.[21] Early and accurate diagnosis of meningitis with CE T2 FLAIR would be useful for efficient management of the patients. Based on the above discussion, it can be concluded that CE-FLAIR sequence can be included in routine MRI protocols for early detection of infective meningitides because of its higher sensitivity, diagnostic accuracy and stronger tie-in with CSF parameters.

CONCLUSION
Results of this study showed higher sensitivity and specificity for contrast enhanced T2 FLAIR in diagnosing infective meningitis. So, use of contrast enhanced T2 FLAIR can be helpful in early screening and diagnosis of meningeal infections when clinically indicated.

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