Comparison of Gadolinium Based T1 Weighted and Flair Mr Sequences for the Assessment of Leptomeningeal Enhancement in Meningoencephalitis

Mubashar Ahmed

AIM: To compare the sensitivity and specificity of post contrast T1W sequence with post contrast FLAIR sequence of MRI brain for early detection of leptomeningitis.

METHODS: A prospective comparative study was conducted for a period of 4 months. MRI brain examination was performed on 55 patients with suspicion of meningitis. Out of these, 48 patients were male and 7 were female. For those patients, contrast enhanced MRI brain with post contrast T1W sequence and post contrast FLAIR sequences were acquired. Then MRI findings were compared with CSF analysis results which was taken by lumbar puncture and considered as a "reference standard".

RESULTS: On CSF analysis of 55 patients, 43 patients were diagnosed positive as having meningitis and 12 patients were negative. Out of these 43 patients, post contrast FLAIR sequence was positive in 41 patients and 33 patients were positive on post contrast T1W sequence. In the finding of meningitis, post contrast FLAIR sequence sensitivity was 95.3% and specificity was 83.3%. While, post contrast T1W sequence sensitivity was 76.7% and 75% was specificity.

CONCLUSION: The sensitivity and specificity of post contrast FLAIR sequence is more as compared to post contrast T1W sequence in the diagnosis of meningitis. In suspected cases of meningitis post contrast FLAIR sequence should be used as a routine sequence for the diagnosis of meningitis.

Key words: CSF; FLAIR; T1W sequences; Meningitis

© 2018 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.


INTRODUCTION

Leptomeninges is the two innermost sheets of tissues that envelop the brain and spinal cord and formed by the layers of arachnoid and pia mater. The arachnoid membrane lies on the dura that is thin and tough membrane at the level of the base of the brain. The brain and spinal cord surface is closely covered by pia mater membrane[1]. Meningitis can be life threatening in the world, if not suspected timely, properly diagnosed and managed[2]. In acute bacterial meningitis, death can be occurred due to the delay in administration of antibiotic. A 4-6 hours delay in the administration of antibiotic can increase the risk of death 8.4 times[3]. Bacterial meningitis is the significant noticeable origin of morbidity in children under 5 years of age[4].

In the evaluation of all kinds of the meningeal diseases, the sensitivity of MR imaging is higher than CT scanning. Moreover, the invention of Gadolinium base paramagnetic contrast medium in
MR imaging enhances the sensitivity and specificity to assess the meningeal abnormalities[9]. The enhancement of the brain surface is also called as pial or pial-arachnoid enhancement, often referred to as leptomeningeal enhancement[8]. Leptomeningeal enhancement can be seen in following conditions:

Meningitis (Pyogenic, Viral, Tuberculouss & CNS Cryptococcal) Encephalitis, Tumors, Hemorrhage[7].

Post contrast spin echo T1 weighted sequences are being unremarkably used to assess several intracranial pathologies including leptomeningitis. Furthermore, contrast enhancement comes out due to T1 shorting effect (relaxivity). In the last decade, for assessment of leptomeningeal diseases post contrast FLAIR (PCFLAIR) has come into view as effective sequence. Meningeal enhancement easily noticeable on post contrast FLAIR images as compare to T1 weighted images, due to nullification of CSF signals and some degree of T1 relaxivity effect[9].

Fluid-attenuated inversion recovery (FLAIR) is a unique inversion recovery pulse sequence has a long repetition time (TR), echo time (TE) and an inversion time (TI) that efficiently void signals from the cerebrospinal fluid (CSF)[9]. CSF assessment is the most vital phase of the laboratory diagnosis of meningitis. Examination of the CSF abnormalities generated by bacterial, mycobacterial and fungal infections may significantly assist for diagnosis and direct primary therapy[10].

As per our knowledge there is only limited local data available focusing on post contrast FLAIR sequence sensitivity in early findings of leptomeningitis, and hence post contrast T1W sequence are acquired. Hence, by conducting this study, we were able to establish the significance of the post contrast FLAIR for accuracy of early detection of leptomeningitis. Post contrast FLAIR was found to be very helpful in the diagnosis of leptomeningitis and so can be very important for the effective treatment of the disease and hence mortality rate can be reduced due to its early detection.

**LITERATURE REVIEW**

Gadolinium enhanced MRI images were superior as compare to post contrast CT scans to identify the meningeal involvement and its complications. Detect of extracerebral fluid collections ability on MRI is also superior because of free of bony artifacts within the skull. In meningitis, major role of Gd-DTPA is to identify the disruption of the effective blood brain barrier and helps in initial recognition of disease process which might be not possible to detect on CT. Thus, in the detection of leptomeningitis MRI appears to be superior as compare to CT after using contrast[11].

**Anatomy of Meninges**

The outer most layer is dura mater (Figure 1). At the plane of cerebral convexity, it is produced by two layers. The external layer is highly vascularized and matching to the periosteum of the inner table. The internal layer is related to the actual meningeal dura mater. The internal layer is just present at the spinal level and laterally extends into the vertebral foramina to shape the sleeves and dural root.

The arachnoid and pia mater develop the leptomeninges. The arachnoid membrane lies on the dura mater. At the superior level of cerebral convexity it is thin and at the plane of base of the brain it becomes thicker. The plane of the brain and spinal cord is closely covered by pia mater and it is thicker at the spinal level[12].

The meningeal layers are separated by spaces: [13] (Figure 1) the gap located between the inner table and dura is known as epidural space, the interval between the dura and arachnoid is called subdural space and the distance located between the arachnoid and pia is called subarachnoid space which contains the cerebrospinal fluid (CSF). Multiple trabeculae filled the subarachnoid space and expanding between arachnoid and pia membrane, also comprise the basal cisterns[14,15].

**Enhancement mechanism of contrast material**

Intravascular (vascular) enhancement and interstitial (extra-vascular) enhancement of the contrast material is a mixture of two basic processes in the central nervous system (CNS)[16,17]. For intravascular injection for contrast enhanced magnetic resonance imaging (MRI), five gadolinium dependent contrast agents were approved between 1988 and 2004 by the U.S Food and Drug Administration. Vasodilatation or neovascularity or hyperemia and shunting or shortened transit time may reflect due to intravascular enhancement. To protect themselves from plasma protein and inflammatory cells the brain, spinal cord and nerves invent a selectively permeable capillary membrane is called blood brain barrier. After injecting a specific amount of contrast material into a large peripheral vein, rapidly raises the level of blood agents, gradient creates around the capillary and endothelial membrane. Contrast agent will seep out across the vessel wall through free capillary permeability and build up in the perivascular interstitial fluid. Leakage of contrast material prevent by intact blood brain barrier in the brain, spinal cord, proximal cranial and spinal cord. Intravascular enhancement is relative to increase in blood volume and blood flow, whereas interstitial enhancement occurred due to permeability of blood brain barrier[18].

**Normal enhancement pattern on Post contrast FLAIR**

Routine interpretation of normal enhancing structure on post contrast FLAIR imaging can consider as a reference point[19]. However, in the adult availability of literature is rare for evaluation of normal enhancement pattern of brain on post contrast FLAIR imaging.

As per our knowledge and preceding reports in the children, intense enhancement can be observed in the choroid plexus, cavernous sinus and pituitary infundibulum and mild enhancement can be seen in the pineal gland, nasal mucosa/ turbinates and pituitary gland (Figure 2). On pre contrast FLAIR shows delicate changes due to intrinsic T2 prolongation, however, pineal gland, pituitary gland and nasal mucosa/turbinates can be tricky to appreciate on post contrast FLAIR, unlike post contrast T1W images. Most blood vessels might be unable to show enhancement on post contrast FLAIR sequence due to a T2 effect. Additionally, due to T1W effect on post contrast FLAIR images enhancement of normal intracranial structures appears less intense as compare to post contrast T1W images[9].

**Enhancement of abnormal meninges**

Two kinds of abnormal meningeal enhancement configuration can be seen (Figure 3): dura-arachnoid and pia-subarachnoid enhancement[17]. For differential diagnosis, the diffuse or focal nature and location of enhancement is useful[20].

**Pia-subarachnoid enhancement**

The diffuse and focal enhancement of meningeal enhancement configuration is similar. Abnormal leptomeningeal enhancement is only related with meningococcal meningitis when findings are deferred. Abnormal enhancement of meninges is markedly linked with tuberculous and pneumococcal meningitis mostly in the sylvian fissures and suprasellar cistern with addition to the posterior fossa and the high convexities[21,22].
Ahmed M et al. Comparison between CE T1W and FLAIR images for meningitis

Figure 1 Diagram depicting meningeal anatomy and spaces.

Figure 2 Normal enhancement on contrast enhancement FLAIR images.
Abnormal intracranial enhancement of pia-subarachnoid associated frequently with linear enhancement beside the surface of the cord and disperse enhancement on the cauda equine. Complication of the basal meningitis from tuberculosis may be lead by brain infarcts and arteritis. Focal or diffuse enhancement may be associated with meningoencephalitis and viral encephalitis. Pattern of enhancement in leptomeningeal neurosarcoidosis is characterized as similar. Enhancement of intra-axial nodular lesion may engage the brain and cord due to expansion of leptomeningeal process alongside the perivascular spaces. Dural lesions enhancement can also be there\textsuperscript[[22]]. Due to steroid treatment, rapid regression of lesions can occurs frequently\textsuperscript[[23]].

**Cerebrospinal fluid (CSF) (Figure 4)**

Count of WBC $>$ 500/mm$^3$ is distinguishing of a bacterial meningitis with preponderance of neutrophils and count of WBC $>$ 100/mm$^3$ is characteristics of a viral meningitis with preponderance of monocytes. To distinguish bacterial meningitis the levels of CSF glucose are used (where it is decreased, typically $<$ 40 mg/dl) from aseptic meningitis (where the level of glucose mostly unaltered)\textsuperscript[[24]]. Level of CSF glucose decreased due to modification in the physiological functioning of the choroid epithelium as well as from utilization of leukocytes and bacterial pathogens\textsuperscript[[25]]. By level of CSF glucose ($<$ 10 mg/dl) and CSF WBC values ($>$ 7500 cells/mm$^3$) differential diagnosis between chemical meningitis and bacterial meningitis can be possible\textsuperscript[[26]]. Greater than 200 mg/dl level of protein considered extremely significant for bacterial meningitis with interference of the blood CSF or blood brain barrier\textsuperscript[[27]].

**CHAPTER-IV**

**MATERIALS AND METHODS**

**Study Design**

This study regarding the comparison of Post contrast FLAIR and T1 weighted MRI sequences results correlated with CSF analysis was a prospective comparative study.

**Sample Size**

All appropriate patients who fulfilled the inclusion criteria and visited us within four months following the approval of synopsis were included.

**Inclusion Criteria**

Patient refer to the department of magnetic resonance imaging with clinical symptoms of meningitis such as fever, neck stiffness, severe headache, nausea vomiting and altered consciousness were contained in this study.

**Exclusion Criteria**

Any patient who had previous surgical history, contrast or sea food allergy, started prophylactic antibiotics and already known case of meningitis were excluded from the study.

**Location**

The study was conducted in Hamad Medical Corporation, Doha Qatar.

**Equipment**

Siemens Skyra 3T MRI were used during the study.

**Examination Method**

An informed consent was taken from all the patients. The significance for the procedure and risk-benefit ratio was explained in detail to the patient. A brief history and MRI safety checklist were taken. Any additional information received from the referring doctor was also taken into account. After this contrast enhanced T1W and contrast enhanced FLAIR images were acquired. Contrast enhanced T1W imaging parameter were: TR: 600, TE: 15, FOV: 230 mm (Adult) or 180 mm (Pediatric), slice thickness: 5 mm (Adult) or 4 mm (Pediatric), slice interval: 1.0 mm, phase encoding direction: R to L.

**Figure 4**

(A) Post contrast T1W coronal MRI shows diffuse, smooth, and linear dura-arachnoid enhancement. Although veins may also enhance normally, there should be no other subarachnoid enhancement; (B) Post contrast Axial T1W MRI of bacterial meningitis. There is diffuse linear superficial (pial) enhancement in the subarachnoid space, extending into sulci (arrowheads) and along the surface of the midbrain.
acquisition time: 2 min 50 seconds.

Contrast enhanced FLAIR imaging parameters were: TR: 9000, TE: 115, FOV: 230 mm (Adult) or 180 mm (Pediatric), slice thickness: 5 mm (Adult) or 4 mm (Pediatric), slice interval: 1.0 mm, phase encoding direction: R to L, acquisition time: 2 min 20 seconds. MR imaging acquired for all patients with intravenous gadolinium contrast medium (the dose was decided according to the patient weight) given by an injector at rate of 0.5 ml/second.

Post contrast T1W and post contrast FLAIR MRI sequences were reviewed by our neuroradiologist to conclude the presence or absence, location and the extension of the abnormal leptomeningeal enhancement in sulci, cisterns or ventricles. The researcher was recorded this data on performa as enhanced (Positive) or non-enhanced (Negative).

CSF analysis results were obtained from laboratory records for final diagnosis of meningitis and recorded by researcher on performa as positive or negative.

Research methodology and statistical analysis

This research was conducted according to the recommended scientific methods. Relevant information was collected from different sources such as reference textbooks, Internet services and scientific magazines. Data was collected first on individual patient data sheets and was then tabulated in data collection sheets. Each patient was designated an individual ID and names were not mentioned. No names and individual patient detail was published. All data collected during the study was stored in a personal computer. The collected data was evaluated and results were acquired using the statistical package for social science (SPSS). For diagnostic accuracy of meningitis on contrast enhanced T1W and contrast enhanced FLAIR images calculated by frequency in terms of enhanced (Positive) or non-enhanced (Negative). The level of significance was considered, if P value equal to or less than 0.05. CSF analysis reports were taken as the reference standard to determine the sensitivity, specificity.

RESULTS

During the period of selection, total 55 patients refer to MRI department with suspicion of meningitis clinically. MRI was done for all the patients and the results were summarized in the tables below.

Out of 55 patients, 48 patients (87.3%) were male and 7 patients (12.7%) were female (Table 1). The mean as per age were 9.2 ± SD 6.08, years ranging from 12 days to 76 years. The distribution of age among patients is shown in table 2.

After MRI examination, for confirmation of the diagnosis of meningitis each patient experiences a lumbar puncture for CSF analysis. Out of 55 patients, 43 patients (78.2%) had CSF positive for leptomeningitis and 12 patients (21.8%) had CSF negative (Table 3). Out of 43 patients in which CSF analysis was positive, on MRI post contrast FLAIR sequence meningeal enhancement was observed in 41 cases (95.3%) and on post contrast T1W sequence meningeal enhancement was observed in 33 cases (76.7%) (Table 4).

Of the 12 cases in which CSF was negative, 10 cases (83.3%) were observed negative on MRI post contrast FLAIR sequence and 9 cases (75%) were shown negative on MRI post contrast T1W sequence (Table 5).

According to CSF analysis results, the sensitivity of post contrast FLAIR sequences was (95.3%), (83.3%) specificity, (95.3%) positive predictive value and (83.3%) negative predictive value while post

Table 1 Gender distribution of the patients (n = 55).

<table>
<thead>
<tr>
<th>Gender</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>48</td>
<td>87.3</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>12.7</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2 Age Distribution of the patients (n = 55).

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-15</td>
<td>7</td>
<td>12.7</td>
</tr>
<tr>
<td>16-30</td>
<td>15</td>
<td>27.3</td>
</tr>
<tr>
<td>31-45</td>
<td>17</td>
<td>30.9</td>
</tr>
<tr>
<td>46-60</td>
<td>10</td>
<td>18.2</td>
</tr>
<tr>
<td>61-75</td>
<td>5</td>
<td>9.1</td>
</tr>
<tr>
<td>76-90</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>Mean and S.D.</td>
<td>9.2 ± 6.08</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 3 CSF analysis results of the MRI cases (n = 55).

<table>
<thead>
<tr>
<th>CSF Results</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>43</td>
<td>78.2</td>
</tr>
<tr>
<td>Negative</td>
<td>12</td>
<td>21.8</td>
</tr>
</tbody>
</table>

Table 4 Results of MR reading for leptomeningitis in positive CSF cases (n = 43).

<table>
<thead>
<tr>
<th>Post contrast T1W MR</th>
<th>Post contrast FLAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced (Positive)</td>
<td>33</td>
</tr>
<tr>
<td>Non-enhanced (Negative)</td>
<td>10</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>76.7% (33/43)</td>
</tr>
</tbody>
</table>

Table 5 Results of MR for leptomeningitis in negative CSF cases (n = 12).

<table>
<thead>
<tr>
<th>Post contrast T1W MR</th>
<th>Post contrast FLAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-enhanced (Negative)</td>
<td>9</td>
</tr>
<tr>
<td>Enhanced (positive)</td>
<td>3</td>
</tr>
<tr>
<td>Specificity</td>
<td>75% (9/12)</td>
</tr>
</tbody>
</table>

Table 6 Comparison between this study and other studies highlighting importance of post contrast FLAIR in the diagnosis of meningitis.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Post Contrast Flair</th>
<th>Post Contrast T1w</th>
<th>Non-Contrast Flair</th>
<th>Post-Contrast T1w Fat Sat</th>
</tr>
</thead>
<tbody>
<tr>
<td>This Study</td>
<td>More Sensitive</td>
<td>Less Sensitive</td>
<td>:</td>
<td>:</td>
</tr>
<tr>
<td>Wanerat Galassi et al (2005)</td>
<td>Less sensitive than contrast enhanced T1W Fat Sat</td>
<td>:</td>
<td>More sensitive than contrast enhanced FLAIR</td>
<td>:</td>
</tr>
<tr>
<td>Singer et al (1998)</td>
<td>Less sensitive than non-contrast FLAIR</td>
<td>More sensitive than post contrast T1W</td>
<td>:</td>
<td>:</td>
</tr>
</tbody>
</table>
contrast T1W sequence observed a sensitivity of (76.7%), (75%) specificity, (91.7%) positive predictive value and (47.4%) negative predictive value (Figure 5). On post contrast FLAIR sequence meningeal enhancement was more extensive with comparison of post contrast T1W sequence (Cases 2 and 3).

As far as etiology concerned, on MRI no specific findings were registered to differentiate between viral, bacterial or fungal meningitis. However, the leptomeningeal enhancement was situated in basal and subarachnoid cisterns in tuberculous and fungal meningitis and in bacterial meningitis; the enhancement was placed over the cerebral convexity and in sylvian fissure.

To compare the frequency of detection of meningitis by post contrast FLAIR and post contrast T1W by using the McNemar test to see the level of statistical significance at 95% confidence interval; obtained a p value of 0.01 ($p = 0.01$).

After this, we have sufficient evidence to conclude that post contrast FLAIR images is better than post-contrast T1W images for the diagnosis of meningitis.

**DISCUSSION**

For early detection of leptomeningitis a favorable clinical outcome is important. For its diagnosis, CSF examination remains as a gold standard or an invasive procedure is compulsory. In clinical imaging like MRI has been established to be useful in detection of leptomeningitis\(^\text{28}\). Routinely T1W conventional sequences been used for diagnosis of meningitis. Better visualization of inflamed meninges, post contrast FLAIR images have shown superior as compare to post contrast T1W images. Post contrast FLAIR images have less cortical veins enhancement, it is allows better feature between enhancing leptomeninges and enhancing cortical veins\(^\text{29}\).

In this study frequency of contrast enhanced FLAIR is almost comparable to Aneel Kumar Vaswani et al\(^\text{29}\). Out of the total 57 patients, 50 were detected as meningitis on CSF examination. Of these 50 patients, 49 patients were diagnosed meningitis on post contrast FLAIR images which is 96%. However, only 34 patients were diagnosed meningitis on post contrast T1W images which is 68%. Whereas, in our study, post contrast FLAIR images have sensitivity of 95.3% and sensitivity of post contrast T1W images is 76.7%. This variation in results between these two studies could be due to technique or number of patients included in the study. But the hypothesis of their and our study is similar; concluding that post contrast FLAIR is a much better sequence in diagnosing meningitis as compare to T1W images (Figure 6).

Waneerat Galassi et al published a study in 2005\(^\text{3}\) showed abnormal meningeal enhancement were positive in 35 post contrast T1W with Fat saturation MR images and in 33 post contrast FLAIR studies. They concluded that post contrast T1W MR images with Fat Saturation is better to post contrast FLAIR imaging in most cases for describing intracranial meningeal disease. The results are different from our study, could be due to the small sample size. In their study total number of patient was only 24. Thirty five examinations were done in these 24 patients. However, 55 patients were included in our study.

In 2015 Armeen Ahmad and his colleagues\(^\text{3}\) conducted a study to determine the discrimination of leptomeningeal and vascular enhancement on post contrast FLAIR for early detection of infectious leptomeningitis. This study suggests that post contrast FLAIR sequence has significant meningeal enhancement and insignificant component of vascular enhancement. The overall qualitative accuracy was 90.3% for post contrast FLAIR match up to 54.8% for

**Figure 4** Diagram shows the collection of CSF fluid through lumbar puncture.

**Figure 5** The results of this study shows comparison between post contrast T1W and FLAIR MRI by bar chart.
post contrast T1W with fat saturation sequence. The sensitivity and specificity was not estimated like our study but aims of study were similar (Table 6).

In a research conducted by Falzone et al. (2008), contrast enhanced fluid attenuated inversion recovery (CEFLAIR) versus contrast enhanced spin echo T1-weighted brain imaging. Their results show superiority of contrast enhanced FLAIR images in comparison with contrast enhanced spin echo T1 weighted images in distinguishing enhancing brain lesions. The results are comparable to our study. However, due to their diagnosis of brain lesions included other than meningitis, exact comparison cannot be made.

A study done by Singer et al in 1998 and his fellows reported that non contrast FLAIR sequence to be superior in comparison with post contrast T1W sequence. The diagnosis of meningitis on FLAIR depends on the protein concentration in CSF that could cause the difference in observation. So, it is possible that protein concentration in CSF could have made more sensitive. In studies which concluded that post contrast T1W images are better as compare to non-contrast FLAIR images could have less CSF protein concentration. Different sample size, different imaging parameters and different MRI machines with different specifications could be other reasons.

Case No. 1. Comparison between the image 1 and 2. Image 1: Post contrast T1W image shows no evidence of Leptomeningeal enhancement.

Case No. 2. Comparison between the image 3 and 4. Image 3: Post contrast FLAIR image shows extensive abnormal Leptomeningeal enhancement along the right frontoparietotemporal Convexity (easily appreciate as compare to T1W).
CSF signal increased in the majority of the patients, after I.V injection when FLAIR sequences were obtained. After gadolinium injection an increased signal of the CSF was shown in all the patients with pathologies direct to a breakdown of the blood-brain barrier or with new vessel configuration close to the ventricles or SAS\textsuperscript{32}.

Finally the results of my study for diagnosis of meningitis encourage the use of post contrast FLAIR sequence due to high sensitivity and specificity as compare to T1W sequence.

**CONCLUSION**

For early detection of meningitis, post contrast FLAIR sequence is significantly better as compare to post contrast T1W sequence. Hence, post contrast FLAIR sequence should be added as a routine sequence in MRI protocol and it can be helpful for making non-invasive provisional diagnosis of meningitis.