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Original Article

Radiology Section

Diffusion Tensor Imaging Parameters in Patients with Meningitis: A Case-control Study

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ABSTRACT

Introduction: Neuroimaging plays an important role in the assessment of meningitis, but conventional Magnetic Resonance Imaging (MRI) is insensitive for early and specific diagnosis. Diffusion Tensor Imaging (DTI) can illustrate disturbances in white matter integrity before they become obvious on conventional MRI.

Aim: To determine DTI parameters, specifically Fractional Anisotropy (FA) and Apparent Diffusion Coefficient (ADC), in patients with meningitis and compare them with controls.

Materials and Methods: This case-control study was conducted over a period of 18 months at Teerthanker Mahaveer Medical College and Research Centre in Moradabad, Uttar Pradesh, India. The study included a total of 61 clinically diagnosed meningitis patients, aged 18 years and above, who were referred to the Department of Radiodiagnosis for an MRI Brain. Additionally, 61 controls were included. Conventional MRI images were obtained followed by DTI. FA and ADC values were calculated by placing Regions Of Interest (ROI) at different levels for both groups. DTI parameters for different causative organisms (bacterial, viral, tubercular, and fungal) were compared. Data was analysed using Statistical Package for the Social Sciences (SPSS) software version 24.0, and Analysis of Variance (ANOVA) test was used to identify significant differences. The p-value <0.05 was considered as statistically significant.

Results: FA values were significantly lower in cases compared to controls at all levels in the brain (mean whole brain FA value of 0.30±0.036 in cases vs 0.43±0.030 in controls). ADC values were significantly higher in cases at the cerebellum, brainstem, and whole brain levels compared to controls (mean whole brain ADC value of 0.812±0.095 in cases vs 0.758±0.026 in controls) (p-value <0.05 considered statistically significant). These differences were evident in patients with clinically proven meningitis who had a normal appearance on conventional MRI, demonstrating the superiority of DTI over conventional MRI for the diagnosis of meningitis. Statistically significant differences were also found among different aetiological agents, highlighting the potential utility of DTI in the differential diagnosis of meningitis cases (mean whole brain FA of 0.31±0.038 in bacterial cases, 0.029±0.037 in viral cases, 0.299±0.034 in tubercular cases, and 0.27±0.00 in fungal cases vs. 0.43±0.030 in controls (p-value <0.01) and mean whole brain ADC values of 0.80±0.051 in bacterial, 0.85±0.14 in viral, 0.79±0.058 in tubercular, 1.03±0.00 in fungal cases vs. 0.758±0.026 in controls (p-value <0.01)).

Conclusion: DTI is more sensitive than conventional MRI and is a useful early indicator of inflammatory process in patients with meningitis.

Keywords: Anisotropy, Apparent diffusion coefficient, Central nervous system infections, Magnetic resonance imaging

INTRODUCTION

Central nervous system infections, such as meningitis, account for about 500,000 deaths worldwide every year, with an expected morbidity and mortality rate of over 95% [1-3]. Despite advances in the field of immunology and pharmacological interventions, case fatality rates remain high, with numbers even more exaggerated among developing countries [4]. Meningitis can be classified based on aetiology into infectious and non infectious causes. Infectious meningitis is further broadly subcategorised into bacterial (pyogenic) and non bacterial causes. Among the latter category are a wide host of pathogens ranging from viral, fungal, and parasitic/protozoal to nosocomial agents [5].

Study mainly focuses on the adult population, specifically above 18 years of age, as immunocompromised elderly patients make up the main mortality victims, with an estimated mortality rate of 3-33% [6,7]. Meningitis is diagnosed based on clinical symptoms, with Cerebrospinal Fluid (CSF) analysis being the mainstay, but only about half of the patients present with the classic triad of fever, altered mental status, and neck stiffness [8,9]. Complicated meningitis cases are associated with paresis, nerve palsies, seizures, motor deficits, and visual and auditory impairments [10]. Neuroimaging has come to play a crucial role in the diagnosis, confirmation, management planning, and follow-up of cases with meningitis. MRI, with its superior soft tissue contrast and anatomical resolution, has proved to be an invaluable tool in the analysis of these patients. Its role also extends to the exclusion of other causes or "meningitis-mimics" such as neoplasms and vascular pathologies [11].

The conventional MR protocol includes T1-Weighted (T1W), T2-Weighted (T2W), Fluid Attenuated Inversion Recovery (FLAIR), and contrast-enhanced T1-Weighted (T1W C+) sequences [12]. Postcontrast meningeal enhancement is considered diagnostic; however, it is found only in about half of the meningitis cases and has been noted in a wide variety of other causes such as neurosarcoidosis, neoplasms, metastasis, carcinomatosis, vasculitis, and neurocutaneous syndromes [11].

DTI is one of the latest and most promising techniques based on the anisotropy of facilitated diffusion of water molecules occurring along the axons. It is a non invasive modality that can make use of the available MRI equipment without the need for any additional contrast or technology [13]. The two most widely used parameters are FA and ADC [14-17]. Based on the degree of this anisotropy, one can detect damage to the white matter fibers on a microstructural level, which occurs in the very initial stages of a disease event, even before these changes become apparent on other MR sequences [18].

Present study aimed to calculate the FA and ADC values in patients with meningitis in different regions of the brain by placing ROI at

the cerebral, cerebellum, and brainstem levels, and then comparing them against those of age- and sex-matched controls. To the best of our knowledge, no other studies have explored the potential utility of DTI in differentiating between different aetiological organisms, which has huge prognostic implications for meningitis treatment.

MATERIALS AND METHODS

This was a case-control study conducted in the Department of Radiodiagnosis at Teerthanker Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh, India, from January 2021 to June, 2022, after obtaining approval from Institutional Ethics Committee (IEC) (TMU/IEC/20-21/035). Prior written informed consent was obtained from the patients.

Cases were defined as patients who were clinically diagnosed with meningitis, characterised by altered mental status, fever, and neck rigidity, with a positive CSF analysis test. They were classified based on aetiology into infectious and non infectious causes. Infectious meningitis was further subcategorised into bacterial, tubercular, viral, and fungal causes.

Inclusion criteria: Patients above 18 years of age who were clinically diagnosed with meningitis, presenting with associated signs and symptoms and CSF analysis were included in the study.

Exclusion criteria: Age <18 years, patients not giving consent, patients who were uncooperative during MRI, patients with absolute contraindications to MRI were excluded from the study.

Sample size: Due to the ongoing Coronavirus Disease-2019 (COVID-19) pandemic, final sample size of 61 cases was achieved.

A total of 61 controls were included in the study, who were patients referred to the department for an MRI brain for other reasons, such as a headache, and who had a normal conventional MRI brain.

Image acquisition: All patients were examined with a 1.5 Tesla Siemens Magnetom Avanto machine. Conventional MRI images were obtained first, followed by DTI. T1-weighted 3D MPRAGE (Magnetisation-Prepared RApid Gradient-Echo sequence) images were obtained with a repetition time (TR) of 2200 ms, echo time (TE) of 2.63 ms, flip angle of 8°, Field of View (FOV) of 256 mm, matrix size of 256×256, 176 slices per slab with a thickness of 1 mm/slice. The DTI was acquired using a single-shot echo-planar sequence with a TR of 3300 ms, TE of 86.0 ms, FOV of 230, matrix size of 128×128, 25 slices with a thickness of 5 mm/slice, and diffusion weighting b-factor of 1000 s/mm^2.

DTI processing was performed, and FA and ADC maps were computed. Tensor images were superimposed on T1 MPRAGE images. Colour-coded FA maps were obtained, where red-coloured tracts represent fibers oriented from left to right, blue from superior to inferior, and green from anterior to posterior. Findings associated with meningitis were assessed on conventional scans, and corresponding ROIs were placed on color-coded maps.

ROI were placed at the Frontal (R), Frontal (L), Parietal (R), Parietal (L), Temporal (R), Temporal (L), Occipital (R), Occipital (L), Cerebellum, Medulla, Midbrain, and Pons. These ROI were placed in the periventricular white matter at the level of the body of the lateral ventricle in the frontal and parietal lobes; at the level of the occipital horns in occipital lobes and at the level of temporal horns in temporal lobes. In cases with identifiable lesions like abscesses and granulomas on conventional MRI brain, additional ROIs were placed at the periphery of the lesion.

After the acquisition of images, they were interpreted by a junior resident and a senior consultant (with 12 years of experience), and the findings were recorded on a predefined proforma, along with the CSF parameters and FA and ADC values.

STATISTICAL ANALYSIS

Data was analysed using SPSS software version 24.0 and ANOVA test was used to identify significant differences. Comparisons between cases and controls were made using an Unpaired t-test and the level of significance was set as <0.05.

RESULTS

Sixty-one patients with clinically confirmed cases of meningitis were included in the study and were compared with 61 controls. Of the 61 cases, 26 (42.6%) were males and 35 (57.4%) were females, with a mean age of 29.00±10.953 years. In the control group, there were 22 (36.1%) males and 39 (63.9%) females, with a mean age of 33.62±14.662 years. There was no significant difference in mean age between cases and controls, as determined by the unpaired student t-test (p-value >0.05).

Among the 61 cases included in the study, 10 (16.39%) were diagnosed as bacterial based on CSF and clinical findings, 18 (29.51%) as viral, 32 (52.46%) as tubercular, and 1 (1.64%) as fungal.

Comparison of mean FA values among the study groups: The mean FA values at the cerebrum, cerebellum, brainstem, and whole brain levels were compared between cases and controls using an unpaired t-test. They were found to be significantly lower compared to controls at all levels (as shown in [Table/Fig-1]).

Variables	Case	Control	t-test	p-value
	Mean±SD	Mean±SD		
Cerebral FA	0.32±0.054	0.51±0.035	29.31	<0.01*
Cerebellar FA	0.218±0.049	0.33±0.055	49.65	<0.01*
Brainstem FA	0.39±0.041	0.45±0.032	4.86	0.007*
Whole brain FA	0.30±0.036	0.43±0.030	22.38	<0.01*

[Table/Fig-1]: Comparison of mean FA among the study groups.
*statistically significant

Comparison of mean ADC values among the study groups: There was no significant difference in the mean cerebral ADC values between cases and controls. However, the mean cerebellar, brain stem, and whole brain ADC values in cases were significantly higher compared to controls (as shown in [Table/Fig-2]).

Variables	Case	Control	t-test	p-value
	Mean±SD	Mean±SD		
Cerebral ADC	0.82±0.06	0.81±0.027	1.06	0.30
Cerebellar ADC	0.76±0.11	0.698±0.062	12.57	0.001*
Brainstem ADC	0.786±0.071	0.763±0.037	5.72	0.018*
Whole brain ADC	0.812±0.095	0.758±0.026	18.31	<0.01*

[Table/Fig-2]: Comparison of mean ADC values among the study groups.
*statistically significant

Comparison of whole brain FA and whole brain ADC according to aetiological agents among the cases: Statistically significant differences in mean whole brain FA and ADC values were found among cases with different causative organisms: bacterial, viral, tubercular, and fungal (as shown in [Table/Fig-3]).

Diagnosis		Mean whole brain FA	Mean whole brain ADC
Bacterial	Mean±SD	0.31± 0.038	0.80±0.051
Viral	Mean±SD	0.296± 0.0377	0.85±0.14
Tubercular	Mean±SD	0.299± 0.034	0.79±0.058
Fungal	Mean±SD	0.27±0.00	1.03±0.00
Anova test		24.17	10.18
p-value		<0.01*	<0.01*

[Table/Fig-3]: Comparison of whole brain FA and whole brain ADC according to aetiological agents among the cases.
*statistically significant

Findings consistent with meningitis on conventional MRI: Out of 61 only 34 (55.7%) cases showed positive findings on conventional scans, whereas 27 (44.3%) cases with confirmatory CSF findings were found to be normal on conventional scans.

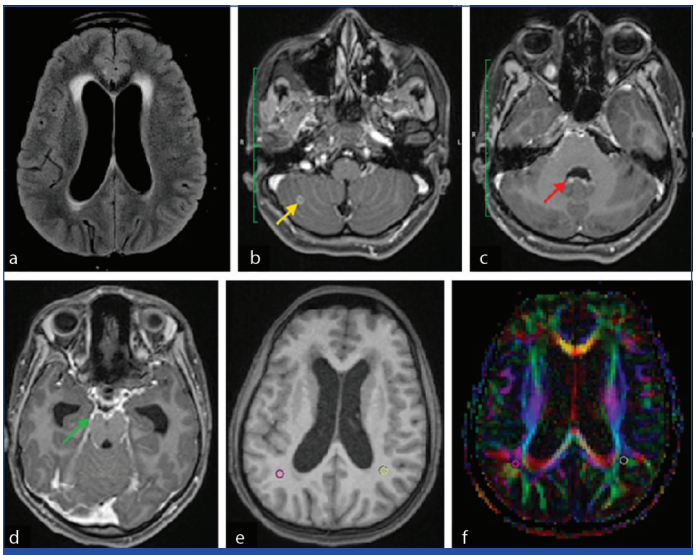
Comparison of DTI values in cases showing normal conventional scans with controls: Among the 27 cases that showed no abnormal findings on conventional MRI scans, comparisons of mean whole brain FA and ADC were made between these cases and controls using an unpaired t-test. The mean whole brain FA value in these cases was significantly lower, and the mean whole brain ADC value was significantly higher compared to controls (as shown in [Table/Fig-4]).

Variables	Cases without findings Mean±SD	Cases with findings Mean±SD	Controls Mean±SD	t-test	p-value
Mean whole brain FA	0.303±0.036	0.298±0.034	0.43±0.030	13.63	<0.01*
Mean whole brain ADC	0.811±0.066	0.813±0.114	0.758±0.026	3.66	0.006*

[Table/Fig-4]: Comparison of DTI values between cases 'without findings on conventional MRI', 'with positive findings on conventional MRI' and controls.
*statistically significant

Among the 34 cases that showed findings consistent with meningitis, the corresponding DTI values also demonstrated statistically significant alterations. The mean whole brain FA value in these cases was significantly lower, and the mean whole brain ADC value was significantly higher compared to controls (as shown in [Table/Fig-4]).

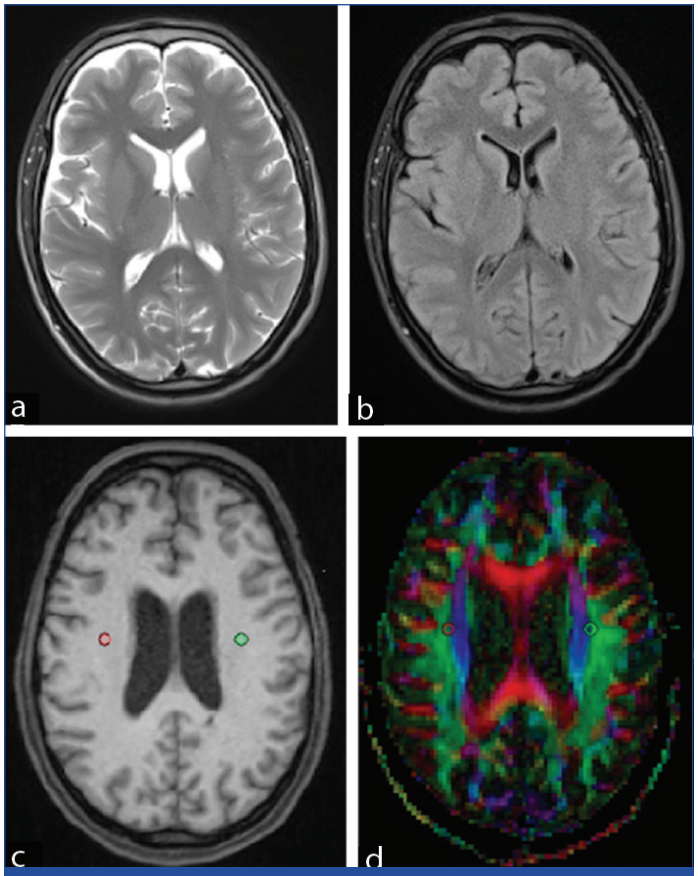
[Table/Fig-5] presents a 22-year-old female clinically diagnosed with tubercular meningitis, showing findings consistent with meningitis on conventional MRI scan. The mean whole brain FA value (0.242) in this patient was significantly lower compared to controls (0.43±0.030), while the mean whole brain ADC value (0.788) was significantly higher compared to controls (0.758±0.026).



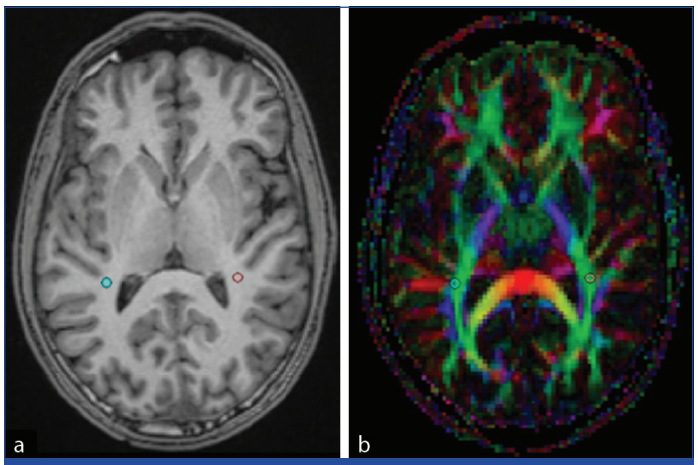
[Table/Fig-5]: a) FLAIR image showing hydrocephalus with periventricular CSF seepage; b) Postcontrast T1W image showing a ring enhancing lesion (arrow) in right cerebellar hemisphere; c) Postcontrast T1W image showing exudates along the floor of fourth ventricle (arrow); d) Postcontrast T1W image showing abnormal meningeal enhancement (arrow); e,f) Region of interest placement at bilateral parietal lobes with corresponding FA colour map.

[Table/Fig-6] shows a 33-year-old male clinically diagnosed with viral meningitis, with a normal conventional MRI scan. The mean whole brain FA value (0.273) in this patient was significantly lower compared to controls (0.43±0.030), while the mean whole brain ADC value (0.840) was significantly higher compared to controls (0.758±0.026).

[Table/Fig-7] displays a normal control for comparison, a 21-year-old male patient presenting to the department for an MRI brain for headache, showing normal conventional MRI. The mean whole brain FA value was 0.434, and the mean whole brain ADC value was 0.765.



[Table/Fig-6]: a,b) Normal non-contrast enhanced T2W and FLAIR images; c,d) Region of interest placement at bilateral frontal lobes and corresponding FA map.



[Table/Fig-7]: a,b) Region of interest placement at bilateral temporal lobes with corresponding FA map.

DISCUSSION

DTI works based on the principle of facilitated diffusion of water molecules along the axons [13]. It quantifies the anisotropic water movement using parameters like FA and ADC, which act as indirect biomarkers for detecting microstructural damage to fibers.

FA provides an assessment of the diffusion pattern and the tendency of unidirectional water molecule flow. It indicates the degree of anisotropy, where zero represents completely isotropic movement and one represents completely anisotropic movement [19,20]. ADC quantifies the magnitude of diffusion, where elevated values indicate a lower degree of diffusion restriction, indicating more damage to the fibers [21,22].

In present study, the majority of cases were diagnosed as tubercular meningitis, followed by viral, bacterial, and fungal meningitis. This can be explained by the high rates of tuberculosis infection in India [21].

Fractional Anisotropy (FA) values: In present study, the mean cerebral (0.32±0.054), cerebellar (0.218±0.049), brainstem (0.39±0.041), and whole brain (0.30±0.036) FA values in cases were significantly lower

compared to controls. Lin WC et al., also demonstrated decreased FA values in the limbic system and white matter near the globus pallidus region in patients with tubercular and cryptococcal meningitis [22]. They attributed these changes to myelin injury. Malik GK et al., studied neonates diagnosed with meningitis and found decreased FA values in periventricular white matter regions, even in areas appearing normal on conventional scans [23]. They suggested oligodendroglial damage and oxidative damage as possible mechanisms for diffuse white matter involvement. Lu CH et al., also found significantly reduced FA values in the frontal, orbital, and periventricular white matter of cryptococcal meningitis patients [24]. Present study findings are consistent with these studies.

Apparent Diffusion Coefficient (ADC) values: In present study, there was no significant difference in the mean cerebral ADC value between cases (0.82±0.06) and controls (0.81±0.027). However, the mean cerebellar (0.76±0.011), brainstem (0.786±0.071), and whole brain (0.812±0.095) ADC values in cases were significantly higher compared to controls. Lu CH et al., also reported similar findings of increased ADC in the genu of the corpus callosum, frontal, parietal, periventricular, and globus pallidus regions [24].

Lin WC et al., found increased mean diffusivity values in the right para-hippocampal gyrus and right cingulate gyrus in meningitis patients compared to controls, attributing these differences to ischaemic and ensuing gliotic changes [22]. However, they did not find changes in the white matter near the globus pallidus, where FA values were significantly lower compared to controls. They explained this disparity by suggesting that myelin injury contributes to lower FA values rather than gliotic changes, which may not significantly affect ADC values. This was similar to the findings in present study, where significant difference was observed in mean cerebellar and brainstem ADC values compared to controls, but not in cerebral ADC values.

Similarly, Malik GK et al., reported no significant difference in mean diffusivity values between patients with normal and abnormal outcomes compared to controls [23]. They attributed this to the delay between symptom onset and the imaging study, as mean diffusivity is an indicator of acute ischaemia that may show "pseudo-normalisation" in the subacute stage. This could be a reason why present study also did not find a significant difference in mean cerebral ADC values.

When comparing FA and ADC findings among patients with different causative organisms, statistically significant differences were found (p-value <0.01) in mean whole brain FA and ADC values among cases categorised based on CSF findings (bacterial, viral, tubercular, and fungal). This highlights the diagnostic potential of DTI in differentiating between different causative organisms.

However, it is important to note that present study was conducted at a single centre with a relatively small sample size. Authors searched online medical research databases to find previous studies on this topic, such as PubMed, Google Scholar, and ScienceDirect, and found that Lin WC et al., assessed DTI parameters in chronic meningitis cases of two aetiologies (tubercular and cryptococcal), but they discussed findings for chronic meningitis cases as a whole without highlighting differences between the two aetiological groups [22]. To the best of our knowledge, no other studies have specifically investigated the differences between aetiological organisms based on DTI parameters.

A comparison was made between conventional MRI scans and DTI for the assessment of patients with meningitis. Out of the total 61 patients studied, only 34 (55.7%) cases showed positive findings on conventional scans, while 27 (44.3%) cases with confirmatory CSF findings were found to be normal on conventional scans. Among the 27 cases with no abnormal findings on conventional MRI scans, the mean whole brain FA value was significantly lower compared to controls. The mean whole brain ADC value was also significantly higher compared to controls. This highlights the superiority of DTI over conventional MRI scans in detecting white matter changes in meningitis patients. This has significant implications for including DTI sequences in routine imaging protocols, particularly for patients with suspected neuronal pathologies.

Limitation(s)

Firstly, the cohort of cases was relatively modest as it was a single-centre study. Secondly, a significant number of meningitis patients referred for imaging studies were in unstable conditions and had altered sensorium, which made the longer MRI scan times a limitation. Thirdly, many patients diagnosed with meningitis were put on empirical treatment regimens before obtaining imaging scans, and the possible influence on DTI values, which is beyond the scope of this study, could not be assessed. Lastly, follow-up of the patients was not done; therefore, assessments regarding the possible prognostic roles of FA and ADC values could not be made.

CONCLUSION(S)

DTI has the potential to be an excellent modality for evaluating white matter injury in patients with meningitis. It can reliably detect and assess neuronal injury in cases with negative conventional scans. Additionally, DTI has the potential to be used as a tool for differentiating meningitis cases based on aetiology, but future studies are needed to assess its full scope of utility in this field.

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