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Original Article

Radiology Section

Diffusion Tensor Imaging for Interpreting Fractional Anisotropy and Mean Diffusivity in Normal-appearing White Matter of Patients with HIV-associated Neurocognitive Disorders: A Case-control Study

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ABSTRACT

Introduction: {Human Immunodeficiency Virus (HIV)-associated Neurocognitive Disorder (HAND)} affects the everyday functioning of patients. It is usually difficult to diagnose HAND in the outpatient setting as detailed neuropsychological performance testing, such as the International HIV Dementia Scale (IHDS), is required. Neuroimaging techniques hold great promise in the early diagnosis and management of HAND, but there is a paucity of studies on the evaluation of HAND using Diffusion Tensor Imaging (DTI) in the Indian population.

Aim: To investigate DTI and interpret Fractional Anisotropy (FA) and Mean Diffusivity (MD) values in the White Matter (WM) of patients with HAND and compare them with age and sex-matched controls.

Materials and Methods: A case-control study was conducted at the Department of Radiodiagnosis, ABVIMS and Dr. RML Hospital, New Delhi, India, from January 2021 to May 2022. Thirty subjects (15 cases and 15 controls) were included. HIV-positive patients underwent the IHDS to assess cognitive impairment. Magnetic Resonance Imaging (MRI) examination was performed at three tesla using conventional sequences, and DTI was applied. Maps of FA and MD values were generated. Mean FA and MD values of normal-appearing white matter tracts between cases and controls were compared using a t-test. Spearman's correlation test was applied to assess the correlation between IHDS scores and DTI parameters.

Results: The majority of cases in the study were in the age group of 31-40 years, and the mean age of cases was 41.27±11.16 years. The present study revealed significantly lower FA values compared to controls in bilateral Frontal WM, Parieto-occipital WM, genu of the Corpus Callosum (CC), right hippocampal WM, and right corona radiata. The mean MD of bilateral Frontal WM, Parieto-occipital WM, corona radiata, and Hippocampal WM was significantly increased in cases compared to healthy controls. A significant association was found between the IHDS score and FA values of the genu of the CC (rho= 0.7), right corona radiata (rho= 0.7), right Hippocampal WM (rho= 0.9), and MD of the left Parieto-occipital WM (rho= -0.6), and left hippocampal WM (rho= -0.5).

Conclusion: Diffusion tensor MR imaging can detect abnormalities that are missed by routine MR imaging. DTI provides a valuable marker to monitor HIV-associated Central Nervous System (CNS) injury, which can lead to neurocognitive impairment.

Keywords: Cluster of differentiation, Human immunodeficiency virus, International human immunodeficiency virus dementia scale, Magnetic resonance imaging

INTRODUCTION

Human Immunodeficiency Virus (HIV) emerged as a major challenge to world health almost thirty years ago and has challenged scientists and clinicians to combat its vast and devastating impact. While recognised for its direct impact on the cellular immune system through the depletion of infected CD4 lymphocytes, it also has had a broad impact on the nervous system [1]. The term HAND has been used to describe the spectrum of neurocognitive dysfunction associated with HIV infection, including Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND), and HIV-associated Dementia (HAD) [2]. Worldwide, HAND remains a common cause of cognitive impairment and has persisted even in individuals who have received Highly Active Antiretroviral Therapy (HAART) [3]. It is usually difficult to diagnose HAND in the outpatient setting as detailed neuropsychological performance testing, such as Mini-mental State Examination (MMSE), IHDS, etc., is required [4].

DTI, which is non-invasive, is employed in clinical neuroimaging studies [5,6]. It assesses the microstructural integrity of the white matter of the brain. The two commonly derived quantitative measures are FA and MD [7]. FA is a measurement of anisotropic water diffusion that indicates the degree of cellular directionality within fiber tracts and, consequently, the structural integrity. MD, on the other hand, measures non collinear diffusion. A decrease in FA value, which is due to damage in tissue microstructure due to the dementia disease process, can lead to an increase in free water diffusion and hence an increased MD value. The decrease in FA value and increase in MD value are markers of neuronal injury [5].

Fewer studies have examined the white matter microstructure in HIV-infected individuals with cognitive impairment and normal-appearing white matter. Du H et al., conducted a study in 2012 on 10 HIV-positive and 24 HIV-negative individuals who underwent DTI to assess the extent to which HIV had affected their brains. The study revealed that FA was mostly affected among HIV-positive patients in comparison to controls without HIV [8]. Oh SW et al., using Tract-based Spatial Statistics (TBSS), conducted research in 2014 to examine the DTI data across HIV patients with and without HAND. In conclusion, Superior Longitudinal Fasciculi (SLF) microstructures were altered in HIV individuals with HAND compared to HIV patients without HAND [9].

Wright PW et al., used DTI to evaluate the cerebral white matter integrity during the first HIV infection. Blood viral load, CD4 count, and DTI measurements were correlated with markers of Blood Brain Barrier (BBB) degradation, inflammation, and illness duration. This study demonstrated the use of DTI measurements as non-invasive indicators of changes in the white matter associated with HIV infection [10]. Davies O et al., conducted cross-sectional research with 48 HIV-negative controls and 78 HIV-positive patients. On DTI, the HIV group showed significantly higher MD and lower FA than the control group. Higher MD and lower FA on DTI were related to worse cognitive function. According to the study, white matter changes may contribute to HIV-related cognitive impairment [11].

Although few studies using DTI investigations have demonstrated links between abnormalities in white matter FA and cognitive impairment in HIV patients, the literature is scarce in the Indian population. The earliest possible diagnosis of cognitive impairment can be made using DTI, which can provide a more objective method of evaluating neuropathological abnormalities in HIV patients. With the assistance of early diagnosis and a deeper understanding of the pathophysiology, one may create better preventative and therapeutic methods to enhance the quality of life for people with HIV or Acquired Immunodeficiency Syndrome (AIDS).

Hence, the present study was conducted to investigate the FA and MD values in the normal-appearing white matter of patients with HAND and compare them with age and sex-matched controls in the Indian population. The study also aims to correlate the findings of DTI with the IHDS score.

MATERIALS AND METHODS

A case-control study was conducted at the Department of Radiodiagnosis, ABVIMS and Dr. RML Hospital, New Delhi, India, from January 1, 2021, to May 31, 2022. The study included 30 subjects (15 cases and 15 controls) referred from the Department of Medicine. Informed consent was obtained from each participant before enrolment in the study. The study protocol received ethical approval from the Institute's Ethical Committee (No. TP (MD/MS) (1/2020)/IEC/ABVIMS/RMLH 272).

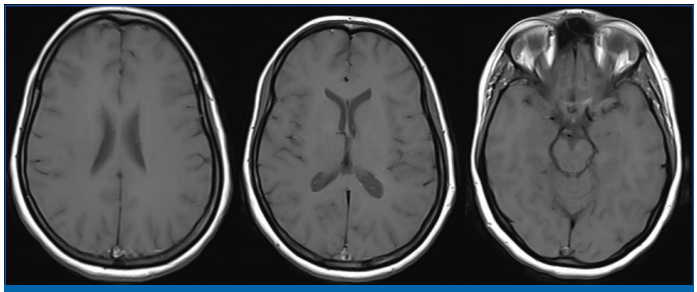
Sample size calculation: The sample size was calculated using online software for a comparative observational study, using reference values from the study by Oh SW et al., for MD [9]. The sample size was calculated using a t-test difference of means of independent groups in the online software G*Power version 3.1. The input parameters included an alpha of 5%, power of 80%, and the sample size calculated to be 24 subjects, with 12 in each group (cases and healthy controls). Finally, to account for any non response, 15 participants in each group were included.

Inclusion criteria: Patients with HAND of both sexes diagnosed using the IHDS were included in the study [4]. Age and sex-matched HIV-negative cognitively normal patients who reported for other MRI examinations were recruited as controls after obtaining voluntary informed consent.

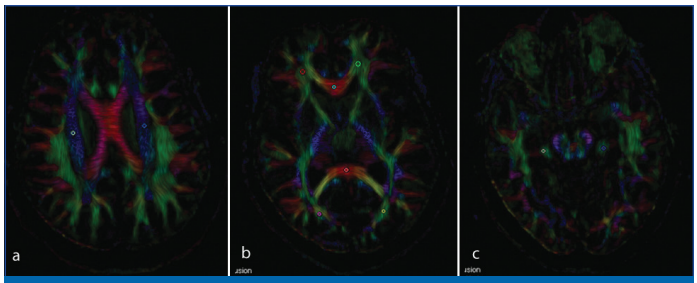
Exclusion criteria: Patients with a history of CNS opportunistic infection, psychiatric illness, brain trauma, neurological illnesses like brain tumour and epilepsy, and patients on steroids or anti-epileptic drugs, etc., were excluded from the study. Patients with contraindications to MR evaluation, such as a history of claustrophobia or presence of ferromagnetic prosthetic devices and implants, were also excluded from the study.

Study Procedure

The MRI examinations were performed using a 3 Tesla scanner with conventional sequences, and DTI was performed with 64 diffusion-sensitising gradients, each with a "b" factor of 0 and 1000 s/sqm. The DTI images were obtained with six averages, 38 slices, a slice thickness of 4 mm, and a Field-of-view (FOV) of 220 mm². Maps of MD and FA were generated using the DTI software (syngo. MR Neuro3D engine). Regions of Interest (ROIs) were carefully placed in normal-appearing white matter in the genu and splenium of the CC, subcortical white matter in bilateral frontal and parietal regions, body of the hippocampus, and corona radiata [Table/Fig-1, 2 (a-c)].



[Table/Fig-1]: Normal-appearing white matter in HIV positive patient with neurocognitive disorder.



[Table/Fig-2]: The Regions of Interest (ROIs) placed in normal-appearing white matter in genu and splenium of Corpus Callosum (CC), subcortical white matter in bilateral frontal and parietal regions, body of hippocampus and corona radiate.

STATISTICAL ANALYSIS

The data was coded and recorded in the MS Excel spreadsheet program. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp). A p-value of <0.05 was considered statistically significant for the difference in FA and MD values of tracts between cases and controls. The variables FA and MD were found to be normally distributed in the two subgroups (cases and controls). Therefore, parametric tests (t-tests) were used for group comparisons. The correlation between IHDS score and DTI parameters was assessed using the Spearman's correlation test.

RESULTS

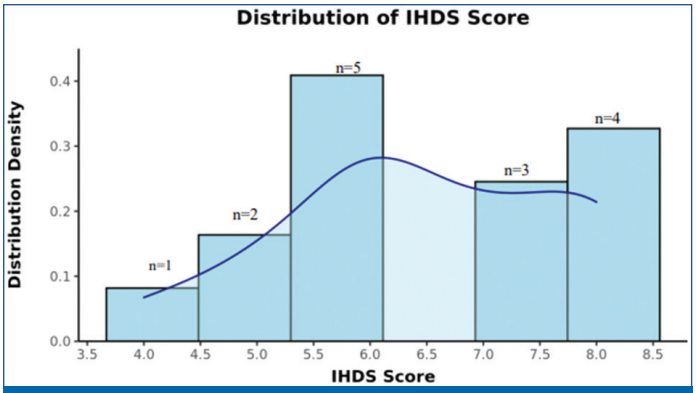
There were no significant age and sex differences observed among the cases and controls in the study. The majority of cases were in the age group of 31-40 years [Table/Fig-3]. The mean age of cases was 41.27±11.16 years. Of the cases, 53.3% were males [Table/Fig-4]. The mean duration of illness was 12.53±8.7 years, and all patients were receiving treatment. In the present study, the IHDS scores ranged from 4-8 [Table/Fig-5].

Age group (in years)	Group			Fisher's-exact test	
	Case n (%)	Control n (%)	Total N (%)	χ^2	p-value
21-30	3 (20.0)	3 (20.0)	6 (20.0)	0.222	1.000
31-40	5 (33.3)	4 (26.7)	9 (30.0)		
41-50	4 (26.7)	5 (33.3)	9 (30.0)		
51-60	3 (20.0)	3 (20.0)	6 (20.0)		
Total	15 (100.0)	15 (100.0)	30 (100.0)		

[Table/Fig-3]: Distribution of the participants in terms of age (N=30).

Gender	Group			Chi-square test	
	Cases n (%)	Control n (%)	Total N (%)	χ^2	p-value
Male	8 (53.3)	7 (46.7)	15 (50.0)	0.133	0.715
Female	7 (46.7)	8 (53.3)	15 (50.0)		
Total	15 (100.0)	15 (100.0)	30 (100.0)		

[Table/Fig-4]: Distribution of the participants in terms of gender (N=30).



[Table/Fig-5]: Distribution of the participants in terms of IHDS (n=15).

The study revealed significantly lower FA values in the study subjects compared to controls in bilateral Frontal WM, Parieto-occipital WM, Genu of CC, Hippocampal WM (Right), and Corona Radiata (Right). The mean MD of bilateral Frontal WM, Parieto-occipital WM, Corona Radiata, and Hippocampal WM was significantly increased in study subjects compared to healthy controls [Table/Fig-6].

Parameters	Group		p-value[1]
	Cases (n=15)	Controls (n=15)	
FA: Frontal WM (Right)*	0.44±0.08	0.52±0.06	0.004
MD: Frontal WM (Right)*	0.76±0.07	0.70±0.05	0.019
FA: Frontal WM (Left)*	0.47±0.05	0.53±0.07	0.009
MD: Frontal WM (Left)*	0.79±0.06	0.69±0.04	<0.001
FA: Parieto-occipital WM (Right)	0.58±0.14	0.60±0.08	0.757
MD: Parieto-occipital WM (Right)*	0.83±0.06	0.72±0.05	<0.001
FA: Parieto-occipital WM (Left)*	0.51±0.13	0.66±0.08	0.001
MD: Parieto-occipital WM (Left)*	0.82±0.07	0.71±0.06	<0.001
FA: Genu of Corpus Callosum*	0.75±0.13	0.83±0.06	0.047
MD: Genu of Corpus Callosum	0.75±0.11	0.70±0.05	0.108
FA: Splenium of Corpus Callosum	0.81±0.08	0.85±0.07	0.290
MD: Splenium of Corpus Callosum	0.72±0.13	0.68±0.08	0.223
FA: Corona Radiata (Right)*	0.45±0.05	0.51±0.06	0.002
MD: Corona Radiata (Right)*	0.73±0.08	0.66±0.06	0.013
FA: Corona Radiata (Left)	0.48±0.07	0.47±0.07	0.867
MD: Corona Radiata (Left)*	0.81±0.08	0.66±0.05	<0.001
FA: Hippocampal WM (Right)*	0.45±0.10	0.61±0.07	<0.001
MD: Hippocampal WM (Right)*	0.81±0.10	0.73±0.08	0.016
FA: Hippocampal WM (Left)	0.52±0.08	0.48±0.08	0.148
MD: Hippocampal WM (Left)*	0.86±0.06	0.75±0.10	0.002

[Table/Fig-6]: Comparison of FA and MD values between cases and controls (N=30). *Significant at p<0.05; 1: t-test

Significant association was found between IHDS score and FA of Genu of CC, right Corona Radiata, right Hippocampal WM and MD of left Parieto-occipital WM, left Hippocampal WM [Table/Fig-7].

Parameters	Spearman's correlation coefficient	p-value
FA: Genu of corpus callosum vs IHDS score	0.7	0.009
FA: Corona radiata (Right) vs IHDS score	0.7	0.002
FA: Hippocampal WM (Right) vs IHDS score	0.9	<0.001
MD: Parieto-occipital WM (Left) vs IHDS score	-0.6	0.032
MD: Hippocampal WM (Left) vs IHDS score	-0.5	0.036

[Table/Fig-7]: Correlation between FA/MD of white matter and IHDS score in (Group: Case) (n=15).

DISCUSSION

The DTI, which is a robust quantitative measure, has the potential to serve as an efficient biomarker for refining the diagnosis of neurocognitive impairment. It assesses the diffusion of water molecules in White Matter (WM) and has gained popularity for evaluating WM microstructure integrity [11,12]. FA reflects water motion deviation and provides information on the structural integrity of highly oriented microstructures, serving as a marker of water molecule diffusion directionality [13]. MD, on the other hand, reflects molecular motion speed and represents average diffusion in all three directions [12].

Previous studies using DTI to evaluate white matter integrity in HIV-positive individuals have shown lower FA values in the genu, splenium, and body of the Corpus Callosum (CC) [14-17]. Some studies have also found elevated MD values in these regions [15-18]. The present study is consistent with these findings, showing lower FA and higher MD values in the splenium of the CC compared to controls, although it was not statistically significant. However, the study did reveal significantly lower FA values in the genu of the CC.

Several previous studies using DTI have evaluated white matter integrity in the corona radiata of patients with HIV-associated Neurocognitive Disorders (HAND), demonstrating increased MD values in various regions [9,17,19]. Some studies have shown significant FA changes as well [20]. The present study is in line with these findings, revealing significantly reduced FA in the right corona radiata and higher MD values in bilateral corona radiata.

Significantly reduced FA values were observed in the right hippocampal white matter, and higher MD values were noted in bilateral hippocampal white matter. This is consistent with studies conducted by Thurnher MM et al., and Li RL et al., [15,18]. The present study also revealed significantly lower FA values in bilateral frontal white matter compared to controls, which is consistent with findings from studies by Thurnher MM et al., and Chen Y et al., [15,21], although the differences were not statistically significant.

Similar to Oh SW et al., the present study also revealed lower FA values in the bilateral parieto-occipital white matter. Specifically, the FA of the left parieto-occipital white matter in cases was significantly lower compared to healthy controls. Although the FA of the right parieto-occipital white matter in cases was lower, the difference was not statistically significant. Moreover, the MD value of the bilateral parieto-occipital white matter was significantly higher compared to healthy controls [9].

The present study had several strengths. Firstly, during the assessment of FA changes, both isotropic and anisotropic voxels were used to avoid any bias in the calculation of FA values. Additionally, texture diffusion maps were utilised for ROI analysis, providing more detailed tract information compared to standard FA maps, resulting in more accurate results for both FA and MD. The findings of the present study demonstrated significant changes in FA and MD within the majority of the investigated tracts in both study groups.

Limitation(s)

In the present study, all patients were receiving HIV treatment, which prevented us from analysing the differences in DTI between treated and untreated patients. After completing the postprocessing of the DTI images, we manually drew ROIs and calculated the mean FA and MD values of the white matter tracts. However, it is important to note that this approach is susceptible to human error, despite ensuring that the ROIs were of appropriate size (30-40 mm^2) to maximise the signal-to-noise ratio.

CONCLUSION(S)

The DTI is a valuable tool for understanding the impact of HIV on the structural integrity of White Matter (WM) and can detect abnormalities that may be missed by routine MRI. Furthermore, DTI may serve as a valuable marker for monitoring HIV-associated CNS injury, which can lead to neurocognitive impairment. To obtain more

robust findings, it is essential to conduct longitudinal studies with larger sample sizes on HIV patients. Such studies would allow us to track the progression of cognitive impairment and assess the effectiveness of treatments.

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