Role of Magnetic Resonance Imaging in Unconscious Patients due to Diffuse Axonal Injury and Its Prognostic Value

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Abstract

Aim To study the long-term prognostic value of early magnetic resonance imaging (MRI) in unconscious patients with traumatic brain injury with findings of NCCT of the brain suggestive of diffuse axonal injury (DAI).

Background Studies addressing the correlation of MRI with the pattern and duration of loss of consciousness due to DAI are few. The utility of MRI in predicting the functional outcome has not been reported in the Indian population.

Materials and Methods In patients with DAI, MRI sequences including T1, T2*GRE (gradient recall echo), fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and susceptibility-weighted imaging (SWI) were obtained. Glasgow coma scale (GCS) and Glasgow outcome scale (GOS) scores were documented at admission, on discharge, and at 3 months.

Results A total of 54 patients (53 males, 1 female) were included in the study. The mean age was 27 $\pm$ 11.7 years. The mean GCS score on admission and at follow-up were 9.14 $\pm$ 2.3 and 11.7 $\pm$ 2.3, respectively. The mean GOS score on discharge and at 3 months were 2.6 $\pm$ 0.8 and 3.18 $\pm$ 1.02, respectively. SWI sequence detected maximum number of lesions followed by GRE and DWI. Patients with lesions in brainstem and basal ganglia were found to have a less favorable outcome as assessed by GCS and GOS at 3 months. There was no correlation between the total lesion load and outcome at 3 months.

Conclusion In patients with DAI, SWI was found to be the most sensitive MRI sequence detecting maximum number of lesions. Patients with lesions in the brainstem and basal ganglia appear to have longer duration of unconsciousness and poorer outcome at 3 months.

Keywords

- diffuse axonal injury
- magnetic resonance imaging
- prognosis
- traumatic brain injury

Introduction

Traumatic brain injury (TBI) has become one the most frequent causes of morbidity and mortality all over the world. It has reached epidemic proportions in India contributing to approximately 1.6 million people seeking medical help and >2 lakh deaths per year. There are >1 million survivors of TBI requiring rehabilitation.[1]

Diffuse axonal injury (DAI) constitutes the major bulk of TBI patients and comprises the most common cause of prolonged comatose or vegetative states. Moreover, patients with DAI constitute a heterogeneous group with some recovering with excellent outcome but others remaining in persistent vegetative state. With the advent of magnetic resonance imaging (MRI), the detection rate of these lesions has increased. The clinical significance of detecting these lesions and their predictive value in terms of clinical outcome has not been assessed in this population. Hence,

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the authors planned to assess the correlation between the locations of lesions on MRI with clinical outcome.

Materials and Methods

The authors prospectively included patients who presented to the Institute of Orthopedics and Traumatology, SMS Medical College and Hospital, Jaipur, India, between February 2015 and September 2016. The authors included patients of all age groups and both sexes with history of head injury having an initial admission Glasgow coma scale (GCS) <12 and findings of computed tomography (CT) of the brain suggestive of DAI. The authors excluded patients with CT findings of epidural hematoma (EDH), subdural hematoma (SDH), or intracerebral hematoma (ICH); patients with associated chest and abdominal injuries; and patients having any history of chronic medical, neurologic, or psychiatric illness. Their demographic, socioeconomic data were recorded. Patients' GCS score was recorded at admission, at discharge, and at 3 months, and Glasgow outcome scale score (GOS) was recorded at discharge and at 3 months after injury to assess their clinical outcome.

After assessing the clinical stability, MRI of the brain was obtained within the first 48 hours of injury. The following special MRI sequences were obtained with 3T MRI machine (Philips Ingenia, the Netherlands) T1, T2* (gradient recall echo [GRE]), fluid-attenuated inversion recovery [FLAIR], diffusion-weighted imaging [DWI], GRE, and susceptibility-weighted imaging [SWI]). Image assessment was done with the assistance of the radiologist who was blinded to the clinical condition of the patient and having experience in TBI imaging. Images were evaluated for the presence of lesions defined as circumscribed foci of signal-intensity abnormality, including hyperintense, hypointense, and mixed hyperintense and hypointense lesions. The signal voids were excluded. The total number of lesions and their locations detected by each sequence were determined separately and recorded. The locations selected included the bilateral frontal lobes, temporal lobes, parietal lobes, occipital lobes, corpus callosum, deep cerebral nuclei (basal ganglia, thalamus), brainstem, and cerebellum.

Statistical Analysis

Data were recorded on a predesigned proforma and managed on Excel spreadsheet. Data were analyzed using SPSS statistical software (ver. 20.0.0; IBM Corp, Armonk, New York, United States). Categorical variables were summarized as frequency (%), and chi-square test was used to compare them between the groups. Quantitative variables following approximately normal distribution were summarized as mean ± standard deviation (SD). The difference between mean was analyzed using ANOVA (analysis of variance) one-way test. Pearson correlation coefficient was calculated to assess the impact of lesion location on the outcome. All statistical tests were two tailed and p values <0.05 were considered significant.

Table 1 Baseline characteristics of patients at admission

Characteristics	n =54
Age (y) mean ± SD (range)	27 ± 11.7 (5–60)
Sex (male:female)	53:1
Mode of injury (%)	
RTA FFH	45 (83.3) 9 (16.6)

Abbreviations: FFH, fall from height; RTA, road traffic accident; SD, standard deviation.

Results

A total of 54 patients were recruited during the study period and followed up for 3 months. Most patients were in their second and third decades. The study population predominantly comprised males except for one. The most common mode of injury was road traffic accident followed by fall from height. The baseline characteristics of the patients at admission were as shown in (►**Table 1**).

Most patients had a low GCS score at admission as shown in ►**Table 1** with GCS <8 ($n = 41$). The GCS gradually improved in a proportion of these patients at discharge and further over 3 months as shown in ►**Table 2**. The other outcome variable that the authors assessed was GOS at discharge and 3 months of injury. Most patients were in persistent vegetative state and severely disabled at discharge. Some of them improved and were minimally disabled at 3 months as shown in (►**Tables 2**, **3**).

Relative numbers of lesions detected by various MRI sequences were as shown in ►**Table 3**. It was seen that SWI was the most sensitive sequence as it detected the maximum number of lesions. This was followed by GRE and DWI as shown in the (►**Table 4**).

Table 2 Patient distribution based on GCS at admission and follow-up

GCS on admission (Mean ± SD: 7.03 ± 1.96)	n
< 8	41
9–13	13
GCS on discharge (Mean ± SD: 9.14 ± 2.3)	
< 8	20
9–13	30
> 13	4
GCS at 3 mo (Mean ± SD: 11.7 ± 2.3)	
< 8	2
9–13	35
> 13	15

Abbreviations: GCS, Glasgow coma scale; SD, standard deviation.

Table 3 Patient distribution based on GOS at follow-up

GOS on discharge (Mean ± SD: 2.6 ± 0.8)	*n*
1	0
2	21
3	25
4	6
5	2
GOS at 3 mo (Mean ± SD: 3.18 ± 1.02)	
1	2
2	11
3	23
4	11
5	7

Abbreviations: GOS, Glasgow outcome scale; GOS1, severe injury or death without recovery of consciousness; GOS2, persistent vegetative state/minimal responsiveness; GOS3, severe disability/conscious but disabled; dependent on others for daily support; GOS4, moderate disability/disabled but independent; can work in sheltered setting; GOS5, good recovery/resumption of normal life despite minor deficits; SD, standard deviation.

The lesions located in the brainstem and basal ganglia showed a significant negative correlation with GCS and GOS scores at 3 months of follow-up (►**Table 5**), whereas corpus callosal lesions showed a significant negative correlation with GCS scores at admission and discharge. These findings suggest that the presence of these lesions probably increases the risk of persistent vegetative state and severe disability. At 3 months follow-up, there were two mortalities. One had lesion in the basal ganglia and corpus callosum and the other had lesion in the brainstem. Both the deaths were caused by acute respiratory infection.

To assess the impact of combination of these lesions on outcome, the authors divided the study population into seven groups based on the locations of lesions: group 1: basal ganglia and corpus callosum (BG/CC); group 2: basal ganglia, brainstem, and corpus callosum (BG/BS/CC); group 3: brainstem and corpus callosum (BG/BS/CC); group 4: brainstem (BS); group 5: basal ganglia and brainstem (BG/BS); group 6 basal ganglia (BG); and group 7 isolated cortical lesions (►**Tables 6**, **7**).

Discussion

Posttraumatic white matter injury was first reported by Holbourn (1943)[2] and by Lidenberg et al (1955)[3] as white

Table 4 Number of lesions detected by various MRI sequences

Sequence	Total No. of lesions	Mean	Median (IQR)
T1	183	3.38	2 (1–5)
DWI	448	8.29	7 (5–10.75)
SWI	754	13.9	11 (8.25–17.75)
T2*GRE	619	11.4	10 (8–14)
FLAIR	263	4.8	4.5 (1.25–8)

Abbreviations: DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; GRE, gradient recall echo; IQR, interquartile range; SWI, susceptibility-weighted imaging.

Table 5 Correlation between lesion location and outcome variables

Correlation coefficient (*p* value)	GCS at admission	GCS at discharge	GCS at 3 mo	GOS at discharge	GOS at 3 mo
Cortical	−0.05	−0.05	0.23	0.13	0.12
	(0.71)	(0.71)	(0.09)	(0.34)	(0.38)
BG	−0.08	0.002	−0.40	−0.08	−0.40
	(0.56)	(0.98)	(0.002)	(0.56)	(0.002)
CC	−0.37	−0.33	−0.09	−0.20	−0.08
	(0.005)	(0.01)	(0.51)	(0.14)	(0.56)
BS	−0.05	−0.06	−0.57	−0.13	−0.57
	(0.71)	(0.66)	(< 0.0001)	(0.34)	(< 0.0001)
Total lesion load	−0.12	−0.10	0.03	0.06	−0.06
	(0.38)	(0.47)	(0.82)	(0.66)	(0.66)

Abbreviations: BG, basal ganglia; BS, brainstem; CC, corpus callosum; GCS, Glasgow coma scale; GOS, Glasgow outcome scale.

Table 6 Patient distribution based on GCS and various combinations of lesion locations

	No. of patients	Group1 BG/CC	Group 2 BG/BS/CC	Group 3 BS/CC	Group 4 BS	Group 5 BG/BS	Group 6 BG	Group 7 Isolated cortical lesions	Total
		5	25	6	7	9	1	1	54
GCS at admission	< 8	4	23	5	5	3	0	1	41
	9–13	1	2	1	2	6	1	0	13
GCS at 3 mo	< 8	0	1	0	1	0	0	0	2
	9–13	2	22	3	3	5	0	0	35
	> 13	2	2	3	2	4	1	1	15

Abbreviations: BG, basal ganglia; BS, brainstem; CC, corpus callosum; GCS, Glasgow coma scale.

matter shearing injury in a group of 51 patients with posttraumatic hemorrhage in the corpus callosum. It was only in 1956 when Strich demonstrated posttraumatic degeneration of white matter and suggested it could be due to white matter shearing injury.[4] The widely used term "diffuse axonal injury" (DAI) was coined in 1982 by Adams et al and Gennarelli et al.[5,6]

DAI is caused by shearing of axons and is typically associated with high-velocity motor vehicle accidents with a component of rotatory acceleration. The shearing is in part due to the difference in inertia between the gray and white matter. This explains the characteristic location of the lesions at the gray-white matter junction and associated rupture of small vessels. The common locations of the lesions include the subcortical white mater, corpus callosum, basal ganglia, upper brainstem, and cerebellum.[7]

DAI has been rapidly evolving as the leading cause of unconsciousness after TBI. Consciousness is composed of two distinct components: awareness and arousal. The primary anatomical locus for arousal is the ascending reticular activating system (ARAS) in the upper pons and lower midbrain. The ARAS is connected to the cortex by three pathways: ventral pathway connecting ARAS to basal fore brain and hypothalamus, dorsal pathway to the reticular nuclei of thalamus, and the direct pathway to the cortex.[8,9] The pathophysiology of unconsciousness in DAI seems to be due to injury to these pathways, which correlates with the location of lesions in DAI.

The following radiologic grading of DAI was given by Adams et al:

- Grade 1 (mild injury): lesions in cortical white matter of frontal and parietal lobes, periventricular lesions
- Grade 2 (moderate injury): lesions of grade 1 with corpus callosum
- Grade 3 (severe injury): lesions of grades 1 and 2 along with lesions in the brainstem[10]

This classification does not emphasize the role of lesion load at individual sites that may affect the outcome, and it also does not provide prognostic information. This study was hence planned in an attempt to assess the prognostic value of the location of lesions in DAI as evidenced on early MRI.

In this study included 54 patients with TBI with initial CT imaging indicative of DAI. This study population comprised predominantly of males (male-to-female ratio: 53:1) in their third to fourth decades (mean age: 27 ± 11.7 years). Road traffic accident was the most common mode of injury ($n = 45$) followed by fall from height ($n = 9$). This is probably due to the higher vulnerability of young males to high-speed motor vehicle accidents. Most patients had a GCS of <8 at admission ($n = 41$) with a mean GCS of 7.03 ± 1.96. (►**Table 1**)

The authors followed up the patients to 3 months and assessed the functional outcome with GCS and GOS. The mean GCSs at discharge and 3 months were 9.14 ± 2.3 and 11.7 ± 2.3, respectively. Of the 54 patients, 41 (75.9%) had a

Table 7 Patient distribution based on GOS and various combinations of lesion locations

GOS at 3 mo	BG/CC	BG/BS/CC	BS/CC	BS	BG/BS	BG	Cortical
GOS 1 ($n = 2$)	1	0	0	1	0	0	0
GOS 2 ($n = 11$)	0	8	0	1	2	0	0
GOS 3 ($n = 23$)	0	13	3	3	4	0	0
GOS 4 ($n = 11$)	4	4	2	0	0	0	1
GOS 5 ($n = 7$)	0	0	1	2	3	1	0
Total ($n = 54$)	5	25	6	7	9	1	1

Abbreviations: BG, basal ganglia; BS, brainstem; CC, corpus callosum; GOS, Glasgow outcome scale.

mean GCS of <8 at admission and the remaining ($n = 13$; 24%) had a GCS of 9 to 13. Most of the patients admitted with severe head injury improved over the duration of stay with 20 (37%) patients remaining with a GCS <8 on discharge. On follow-up at 3 months after injury, only two patients remained with a GCS <8. However, approximately 67% ($n = 35$) of the patients remained in the moderate group (GCS 9–13) reflecting the morbidity of this disease (►**Table 2**).

To assess their short-term functional outcome, GOS was recorded at 3 months. Mean GOS at 3 months was 3.18 ± 1.02. At 3 months 62% of patients remained in GOS of 2 to 3 ($n = 11$ and 23, respectively) with only 7 patients attaining a GOS of 5. This suggests the severity of functional impairment and morbidity, and this was similar to earlier reported literature (►**Table 3**). This degree of functional impairment warrants the search for prognostic markers as intended by this study.

Since the advent of MRI, several studies have reported the superiority of MRI in diagnosing DAI compared with CT.[11–13] Studies have also reported the prognostic significance of lesion load and their locations on MRI.[12,13] SWI was the most sensitive MRI sequence in this study as it detected the maximum number of lesions followed by GRE, DWI, and FLAIR in that order as shown in (►**Table 4**). Similar results were also shown by Abu Hamdeh et al[14] and others.[15–17] This has practical importance in an economically constrained society such as India. A single SWI or DWI (in case of nonavailability of SWI) sequence may reduce the overall cost of health care for these patients with the benefit of detecting the maximum number of lesions. However, further studies on a larger population are required to validate this conclusion.

In this study, the total lesion load was not found to have any significant correlation with the outcome. This is probably due to the fact that the major contribution to the lesion load was by cortical lesions, which did not have any correlation with the outcome. This is in concordance with results by Moen et al and Abu Hamdeh et al.[14,18]

The authors found a significant negative correlation between lesions in the brainstem, basal ganglia, and corpus callosum with the functional outcome (►**Table 5**). Patients with lesions in the brainstem and basal ganglia had poorer GCS and GOS at 3 months, indicating a poorer outcome and longer duration of unconsciousness in these patients. However, patients with lesions in the corpus callosum had a poorer GCS at admission, but no significant correlation was noted with GCS at discharge and 3 months, suggesting a possibility that these patients probably have a better recovery in the long term. The results of this are in concordance with the published studies by Moen et al and Kampfl et al.[18,19] This is also in favor with prime anatomical localization of the center of consciousness ARAS in the brainstem as described previously. It appears that along with the brainstem, lesions in the corpus callosum and basal ganglia add to the severity of unconsciousness as they lie along the awareness pathways connecting the ARAS and the cerebral cortex.[8,9]

Because the authors found a significant correlation with the presence of lesions in the brainstem, basal ganglia, and corpus callosum and functional outcome, they intended to extend their analysis to find the impact of a combination of these lesions on the outcome. For this purpose the authors divided the study population into seven groups (►**Tables 6**, **7**) based on a combination of the location of lesions. Group 2 (BG/BS/CC) was the most frequent combination ($n = 25$) followed by group 5 (BG/BS) ($n = 9$) and 4 (BS, $n = 7$), and rest of the patients almost equally distributed between groups 1 (BG/CC) ($n = 5$) and 3 (BS/CC) ($n = 6$). Because most patients were in group 2 with very few patients in the other groups, subgroup analysis was not feasible. However, as evident from ►**Table 7**, nearly 50% of the patients with any lesion in the brainstem (groups 2–5) remained with severe disability (GOS 3) at 3 months. This reinforces the prognostic significance of brainstem lesions as explained earlier. Because the number of patients with other combination of lesions was very small, larger studies with adequate numbers may help evaluate the actual effect of other lesion locations on the functional outcome.

This study is one of the few studies to correlate the location of lesions with the outcome at a short-term follow-up of 3 months. This study has several limitations that include a small sample size. The authors excluded patients with very severe DAI and those who were hemodynamically unstable due to the technical difficulties in obtaining MRI in these patients. This might have affected the results.

Conclusion

DAI is rapidly emerging as a major cause of prolonged unconsciousness and vegetative state that may reach epidemic promotions in the near future. The fact that the predominant population affected includes young adults adds to the economic burden on the society. Early imaging with MRI and localizing the lesions may help us prognosticate individual patients. This may be of importance as anticipation of prolonged state of unconsciousness may help early institution of intensive care and rehabilitation in these patients. Brainstem lesions alone and more so in combination with lesions in the corpus callosum and basal ganglia as identified on MRI may indicate poorer outcome at 3 months in terms of consciousness and functional recovery. However, as sample size for this study is small, larger studies are required to validate these results.

Note
The study was presented at the Neurotrauma 2016 at AIIMS, New Delhi, India. The study was awarded the Shri J. B. Modi Best Paper Award at the 25th Annual Conference of Neurotrauma Society of India 2016, AIIMS, New Delhi, India.

Conflict of Interest
None.

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