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MRI EVALUATION OF BRAIN MORPHOMETRIC CHANGES AND ALCOHOL-RELATED ENCEPHALOPATHIES IN PATIENTS WITH ALCOHOL USE DISORDER: A CASE-CONTROL STUDY

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ABSTRACT

Aim: The present study was undertaken to evaluate brain morphometric changes detected on magnetic resonance imaging in patients with alcohol use disorder and to compare these findings with age-matched controls. The study also aimed to determine whether the extent of morphometric abnormalities was related to the duration of alcohol consumption.

Materials and Methods: This observational case-control study was carried out in the Department of Radiodiagnosis, SreeBalaji Medical College and Hospital, Chennai. The study population consisted of 80 adult males, including 40 patients with alcohol use disorder and 40 age-matched controls. Alcohol use disorder was diagnosed according to DSM-5 criteria. Participants between 21 and 60 years of age were included. Patients with a history of traumatic brain injury, epilepsy, delirium tremens, dementia, other organic neurological or psychiatric disorders, and claustrophobia were excluded. MRI of the brain was performed using a 1.5-Tesla MRI system. T1-weighted, T2-weighted, FLAIR, diffusion-weighted and ADC sequences were obtained as appropriate. Morphometric assessment included measurements of the ventricles, interhemispheric fissure, cerebral peduncles, pons, medulla, fourth ventricle, cerebellum and different parts of the corpus callosum.

Results: Quantitative comparison of brain morphometric parameters showed differences between patients with alcohol use disorder and the control group. The thesis-derived findings showed enlargement of ventricular spaces and widening of the interhemispheric fissure, along with reduction in selected measurements of the brainstem and corpus callosum among alcohol-dependent individuals. Several of these abnormalities became more prominent with increasing duration of alcohol consumption. MRI also demonstrated characteristic patterns associated with alcohol-related neurological complications, including hepatic encephalopathy, Wernicke encephalopathy, Marchiafava-Bignami disease and osmotic demyelination.
The exact means, standard deviations and p values for the revised cohort of 40 cases and 40 controls should be recalculated from the original individual-level dataset before submission to a journal.

Conclusion: MRI is a useful non-invasive imaging modality for demonstrating structural brain changes associated with chronic alcohol consumption. Quantitative morphometry can demonstrate abnormalities involving the cerebral and cerebellar structures, ventricular system, brainstem and corpus callosum. In addition, conventional MRI with FLAIR and diffusion-weighted sequences can help identify characteristic patterns of alcohol-related encephalopathies.

1.INTRODUCTION

Alcohol use is an important cause of neurological morbidity and can produce a wide range of structural and functional abnormalities within the nervous system. Long-term alcohol exposure may be associated with brain volume loss, nutritional deficiencies and metabolic disturbances. Several neuroimaging studies have described cerebral atrophy, enlargement of the ventricular system and abnormalities involving the white matter, cerebellum, corpus callosum and brainstem in individuals with chronic alcohol use.[1–4]

Magnetic resonance imaging has an important role in the evaluation of alcohol-related brain injury. Its excellent soft-tissue contrast allows detailed assessment of the brain and makes it possible to identify subtle structural abnormalities without exposure to ionizing radiation. Structural MRI has demonstrated changes involving both grey and white matter in patients with alcohol use disorder. White matter structures appear to be particularly vulnerable to the effects of prolonged alcohol exposure.[2,3]

Earlier morphometric studies have described enlargement of the lateral and third ventricles, widening of the interhemispheric fissure and loss of cerebellar volume in individuals with chronic alcohol use.[4,5] Changes involving the corpus callosum have also been reported and may represent the effects of alcohol-related white matter injury.[6]

Apart from chronic structural changes, alcohol use is also associated with several potentially serious neurological complications. These include Wernicke encephalopathy, Marchiafava-Bignami disease, hepatic encephalopathy and osmotic demyelination. MRI is particularly useful in these conditions because many of them have characteristic signal abnormalities on T2-weighted, FLAIR and diffusion-weighted images.[7–10]

Wernicke encephalopathy typically demonstrates symmetrical abnormalities involving the medial thalami, periventricular region around the third ventricle, periaqueductal region and mammillary bodies.[7,8] These findings, when present in an appropriate clinical setting, can help in making an early diagnosis.
Marchiafava-Bignami disease is characterized by demyelination and necrosis involving the corpus callosum. The "sandwich" and "boomerang" signs are recognized imaging patterns associated with this condition.[9] Diffusion-weighted imaging can be particularly useful in demonstrating areas of restricted diffusion.
The present study was therefore undertaken to assess quantitative MRI morphometric changes in patients with alcohol use disorder and compare these measurements with age-matched controls. An additional objective was to determine whether the degree of morphometric alteration was associated with the duration of alcohol intake.

2.AIM AND OBJECTIVES

Aim

To evaluate the role of MRI in detecting degenerative brain changes in patients with alcohol use disorder.

Objectives

To assess brain morphometric parameters in patients with alcohol use disorder.
To compare the measured morphometric parameters with those of age-matched controls.
To evaluate the relationship between brain morphometric changes and the duration of alcohol intake.
To identify MRI features of alcohol-related neurological complications.

3.MATERIALS AND METHODS

Study Design and Setting

The study was designed as an observational case-control study and was conducted in the Department of Radiodiagnosis, SreeBalaji Medical College and Hospital, Chennai, Tamil Nadu, India.

Study Population

The revised study population consisted of:
40 patients with alcohol use disorder, who constituted the case group.
40 age-matched individuals without alcohol use, who constituted the control group.
The original thesis described recruitment of adult male patients diagnosed with alcohol use disorder according to DSM-5 criteria, together with age-matched controls.

Inclusion Criteria

The following participants were included in the study:
Male patients between 21 and 60 years of age.
Patients fulfilling DSM-5 criteria for alcohol use disorder.
Patients willing to undergo MRI examination.
Participants who provided written informed consent. Where applicable, consent was obtained from legally authorized representatives.

Exclusion Criteria

Patients were excluded from the study if they had any of the following:
Age above 60 years.
Previous traumatic brain injury.
Epilepsy.
Delirium tremens.
Dementia.
Other organic neurological disorders.
Other psychiatric disorders likely to interfere with assessment.

Claustrophobia or any contraindication to MRI.
These eligibility criteria were based on the framework described in the source thesis.

OBSERVATIONS

Table I Age Of Cases

AGE (years)	Cases	Percentage
21-30	9	18.0
31-40	16	32.0
41-50	15	30.0
51-60	10	20.0
Total	50	100.0

Table 1 shows the age distribution of the cases. Between the ages of 21-30 years there are 9 patients (18%). Between the

ages of 31-40yrs there are 16 patients (32%). There are 15 patients (30%) between the ages of 41 to 50. Between the ages of 51 to 60 there are 10 patients (20%).

Table Ii Type Of Alcohol Consumed

Type of Alcohol	No. of Patients	Percentage
DesiDaru	6	12.0
Rum	7	14.0
Vodka	2	4.0
Whiskey	28	56.0
Unknown	7	14.0
Total	50	100.0

Table 3 and Figure 3 show the type of alcohol mostly consumed by the patients in the study. It is evident form the table that 6 patients (12%) consumed DesiDaru. 7 patients (14%) consumed Rum. Vodka was preferred by 2 patients (4%). Whiskey was consumed by 28 patients (56%). The status of alcohol consumption was unknown for 7 patients (14%).

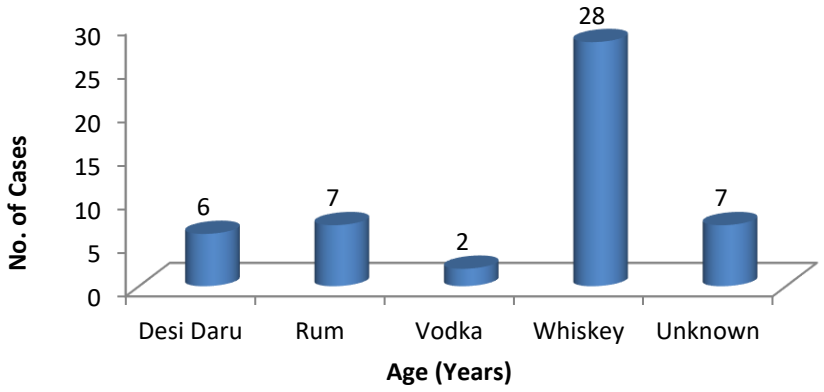


Table Iii. Major Brain Morphometric Parameters Vs Duration Of Alcohol Intake

Group Duration of Alcohol Consumption (in years)	Distance between Anterior horn tips (mm)	3rd ventricle width (mm)	Width of interhemispheric fissure (mm)	Cerebral peduncle width (mm)	A-P diameter of pons (mm)	A-P diameter of Medulla (mm)	Cerebellar transverse length (mm)	Cerebellar vermian length (mm)	Cerebellar vertical length (mm)
<=5	33.13	7.67	7.60	13.92	24.24	13.87	37.36	24.80	39.68
6-10	33.76	7.37	7.26	13.73	22.56	13.62	39.28	26.61	42.58
11-15	35.24	7.37	7.79	13.84	23.47	13.67	38.51	25.84	41.34
16-20	31.25	7.92	6.90	13.48	22.49	13.02	38.65	24.99	39.98
21-25	33.70	7.55	7.80	13.95	19.90	13.05	35.50	21.95	35.12
>25	28.35	8.20	7.95	12.70	19.25	12.10	36.50	22.20	35.52

Here we see a comparison of measurements of various brain parameters against the duration of alcohol intake in years. From the table, it is evident that the distance between the anterior horn tips of the lateral ventricle, cerebral peduncle width, diameter of pons and medulla was the smallest in the group that had been drinking the longest.
Width of the 3rd ventricle and the interhemispheric fissure was the highest in the patients with highest duration of drinking history. Both of these findings suggest that as the number of years of drinking increases, the amount of atrophy of the brain parenchyma increases

Table Iv. Brain Measurements In Cases And Controls

Brain Measurements (mm)	Cases (Mean±S.D.)	Control (Mean±S.D.)	p value
Distance between Anterior horn tips	33.07±3.91	33.58±3.02	$p>0.05^{NS}$
3rd ventricle width	7.61±0.93	6.39±0.34	$p<0.001^{**}$

width of interhemispheric fissure	7.38±0.96	6.45±0.52	$p<0.001^{**}$
cerebral peduncle width	13.69±0.71	13.99±0.71	$p<0.05^{*}$
A-P diameter of pons	22.79±3.89	25.06±1.79	$p<0.001^{**}$
A-P diameter of Medulla	13.43±1.03	13.79±0.91	$p>0.05^{NS}$
IV ventricle height	`13.01±1.26	11.82±1.35	$p<0.001^{**}$
IV ventricle width	17.29±1.19	15.44±1.01	$p<0.001^{**}$
Cerebellar transverse length	38.35±2.33	37.40±2.42	$p<0.05^{*}$
cerebellar vermian length	25.35±2.63	25.58±2.17	$p>0.05^{NS}$
cerebellar vertical length	40.55±4.21	40.67±3.41	$p>0.05^{NS}$
CC Genu	10.08±0.99	10.76±0.88	$p<0.001^{**}$
CC Splenium	10.16±1.40	11.30±0.82	$p<0.001^{**}$
CC Body	4.35±0.75	5.83±0.64	$p<0.001^{**}$

p>0.05=Not-Significant (NS), p<0.05=Significant*, p<0.001=highly significant**
From this table we infer that there were considerable differences in the measurements of certain brain parameters between cases and controls.
The difference however was not significant in:
Distance between anterior horn tips.
A-P diameter of medulla.
Cerebellar vermian length.
Cerebellar vertical length.
The difference was significant (p<0.05) in:
Cerebral peduncle width.
Cerebellar transverse length.
The difference was highly significant (p<0.001) in:
3rd ventricle width.
Interhemispheric fissure width.
A-P diameter of pons.
4th ventricle height.
4th ventricle width.
Genu Corpus Callosum.
Splenium.
Body of Corpus Callosum.

Table Vii. Fourth Ventricular Size In Relation To The Alcohol Intake

Duration of Alcohol intake (years)	Fourth Ventricle size (mm)	
	Height	Width
<=5	12.6	16.7
6-10	12.7	17.3
11-15	12.7	16.7
16-20	13.7	17.9
21-25	13.6	18.1
>25	14.3	18.8

Here we see the relationship of 4^{th} ventricle with the duration of alcohol consumption in years. It is clearly evident from the graph that as the duration of alcohol intake increased, there was increase the 4^{th} ventricle height and width suggesting that there was a proportional reduction in the size of cerebellum and the brainstem volume.

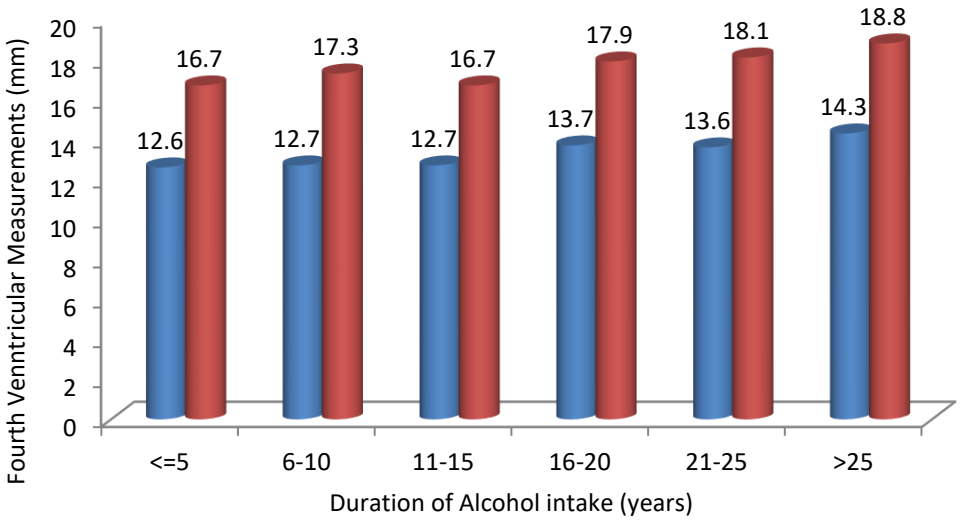
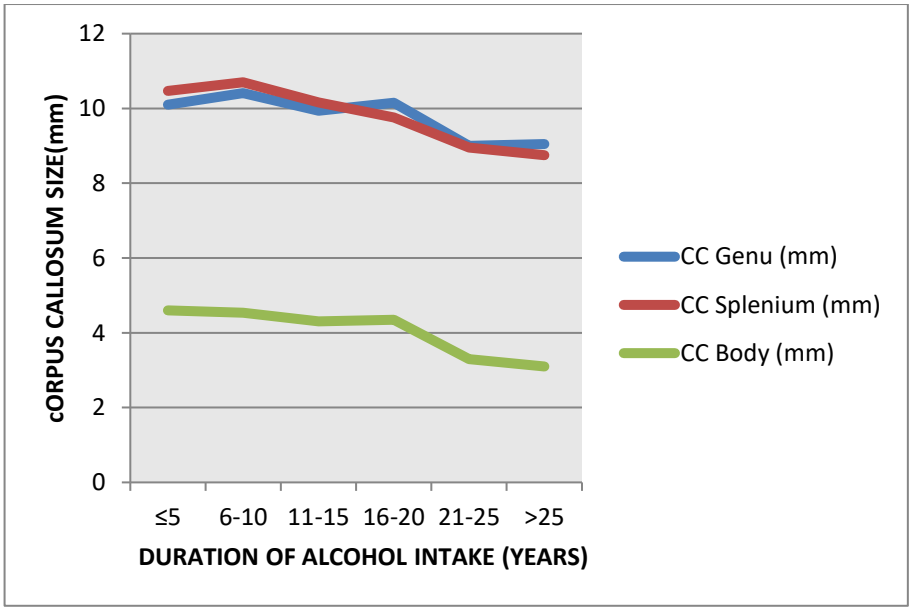


Table Xi. Corpus Callosum Size In Relation To The Duration Of Alcohol Intake

Group Duration of Alcohol intake (years)	CC Genu (mm)	CC Splenium (mm)	CC Body (mm)
≤5	10.10	10.47	4.60
6-10	10.41	10.70	4.54
11-15	9.94	10.16	4.31
16-20	10.15	9.76	4.35
21-25	9.00	8.95	3.30
>25	9.05	8.75	3.10

From the Table and the line diagram, it is evident that there was slight decrease in the Corpus Callosum genu, body and splenial size as the extent of alcohol intake gradually increased. These findings are also illustrated in the line diagram shown below which shows a steep decrease in the corpus callosum size after approximately 20 years of alcohol consumption.



CASES

CASE 1 - HEPATIC ENCEPHALOPATHY

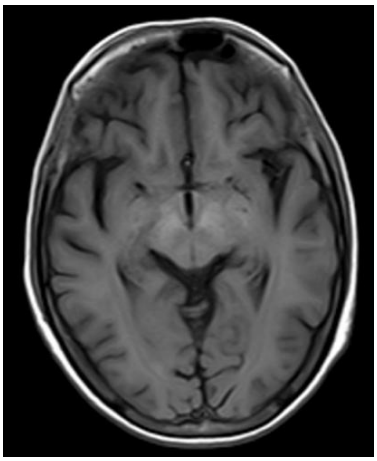


FIGURE A - T1WI

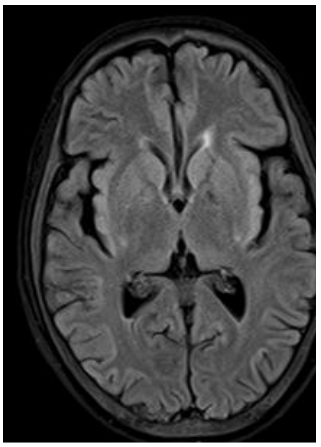


FIGURE B - FLAIR

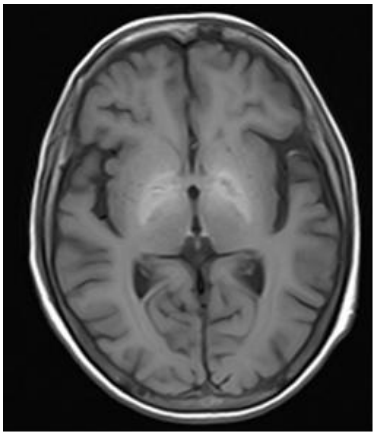


FIGURE C - T1WI

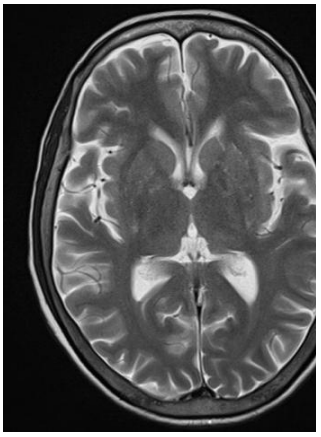


FIGURE D – T2WI

Hyperintensities are seen within B/L Globus Pallidi and B/L cerebral perduncle on T1WI (a) which are characteristic of Hepatic Encephalopathy. Mild hyperintensity is also noted in B/L insular cortex. These subtle hyperintensities are pronounced on the FLAIR images(b).T2WI shows subtle, ill-defined hyperintensity within the Basal ganglia, specially the caudate nucleus & the putamen(d).

Case 2 - Marchiafava Bignami Disease

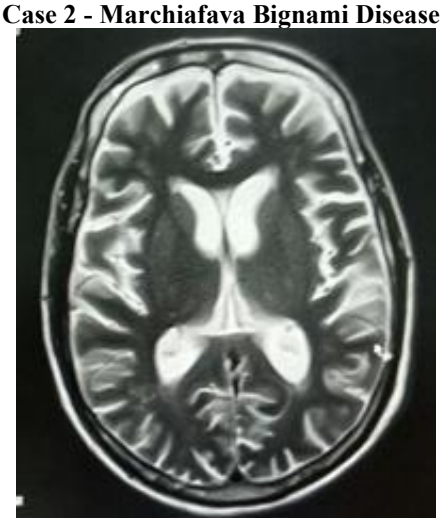


FIGURE A - T2WI

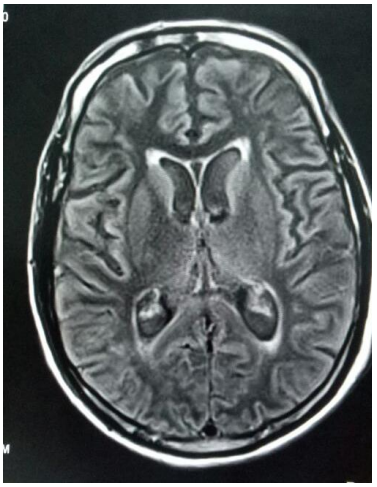


FIGURE B - FLAIR

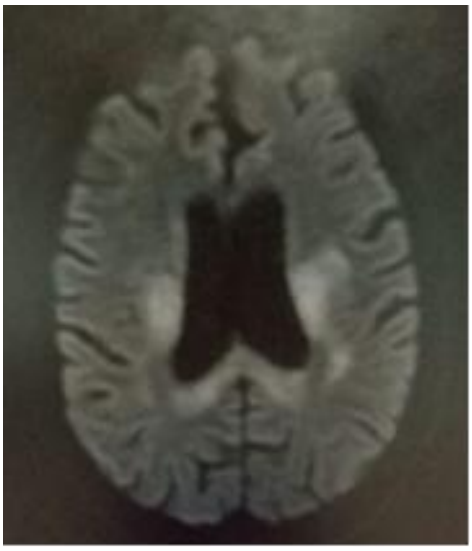


FIGURE C – DWI

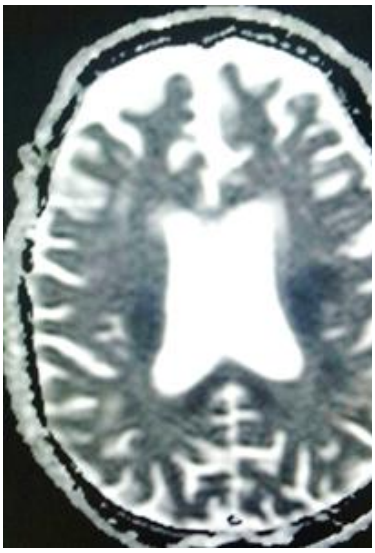


FIGURE D - ADC

Symmetric subtle T2 (a)and FLAIR(b) hyperintensities involving bilateral corona radiata, crus cerebri, posterior limb of B/L internal capsule and splenium of corpus callosum. On DWI/ADC maps, these areas show restriction(c &d). Classic "Boomerang" sign can be seen in the region of the splenium where restriction is present

Case 3 - Marchiafava Bignami Disease

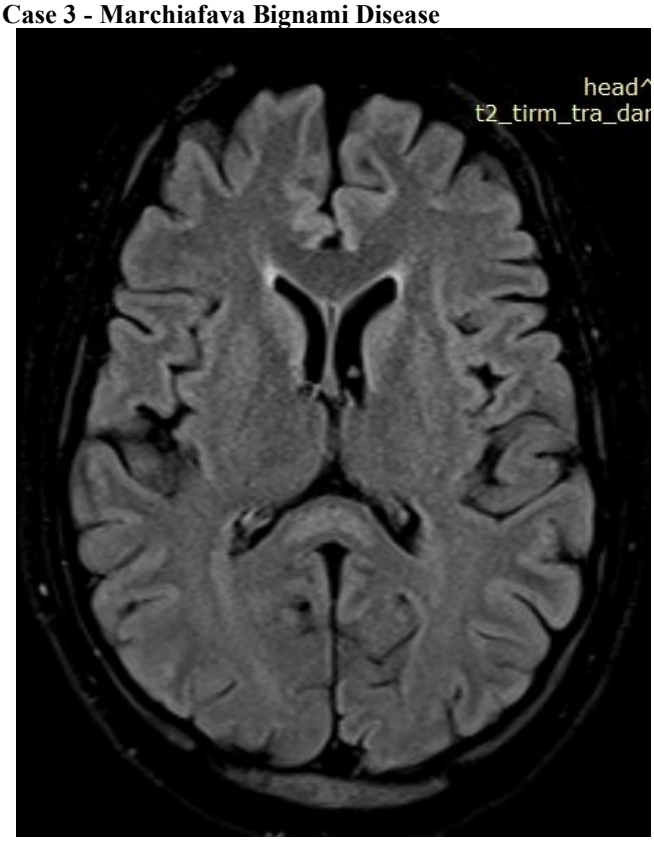


FIGURE A – FLAIR

Some other classic signs described in the literature can be seen in the case shown above.
"Ears of a Lynx Sign" T2/FLAIR cone (triangle) shaped hyperintensity is seen at the tip of the frontal horn of the lateral ventricles which resembles the tufts of hair crowning the ears of a lynx
"Sandwich Sign" - Involvement of the central layers of splenium of the Corpus Callosum.

CASE 4 - OSMOTIC MYELINOSIS



FIGURE A – T2WI

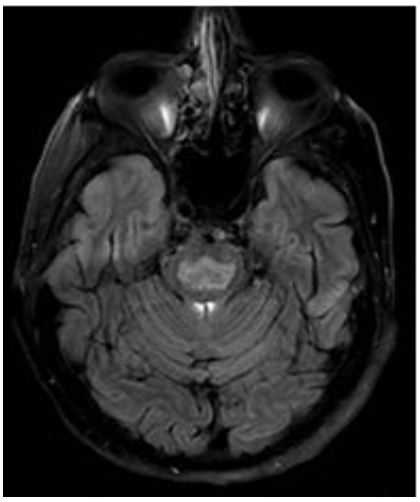


FIGURE B - FLAIR

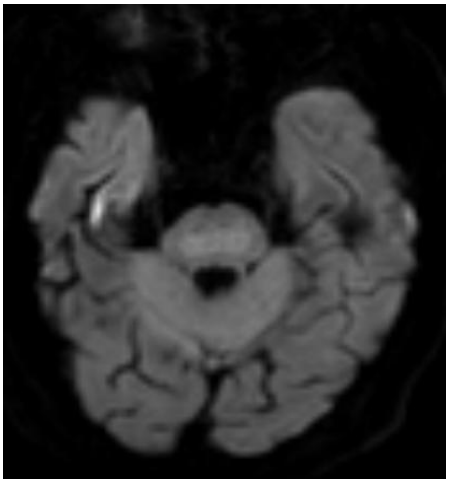


FIGURE C – DWI

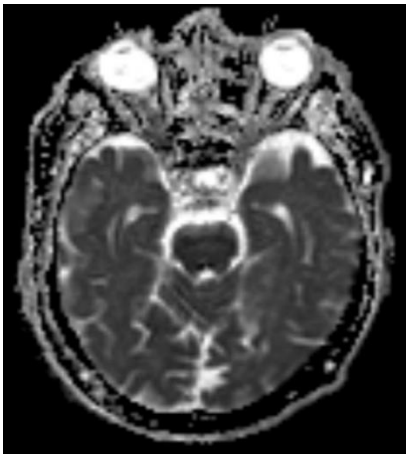


FIGURE D – ADC

Ill defined area of hyperintensity was seen in the central part of pons with peripheral sparing demonstrating the classical "Trident Sign" on T2(a) and FLAIR (b)images. It shows restriction in the form of mild hyperintensity on DWI(c) and hypointensity on ADC(d). – Pontine myelinosis

MRI Technique

MRI examinations were performed using a 1.5-Tesla Siemens MRI system.
The imaging protocol included the following sequences, as appropriate:
Sagittal T1-weighted images.
Axial T1-weighted images.
Axial T2-weighted images.
Coronal T1- and T2-weighted images.
FLAIR images.
Diffusion-weighted imaging.
ADC mapping.
The original study used the same 1.5-Tesla MRI approach and sequence protocol.

Morphometric Assessment

The following brain morphometric parameters were assessed:
Distance between the tips of the anterior horns.
Width of the third ventricle.
Width of the interhemispheric fissure.
Width of the cerebral peduncle.
Anteroposterior diameter of the pons.
Anteroposterior diameter of the medulla.
Height of the fourth ventricle.
Width of the fourth ventricle.
Transverse length of the cerebellum.

Length of the cerebellar vermis.
Vertical length of the cerebellum.
Measurement of the genu of the corpus callosum.

Measurement of the body of the corpus callosum.
Measurement of the splenium of the corpus callosum.
The morphometric assessment included measurements of supratentorial structures on axial T1-weighted images. Brainstem measurements were obtained on sagittal T1-weighted images, while the dimensions of the fourth ventricle and cerebellum were assessed using the appropriate imaging planes. Measurements of the corpus callosum were obtained in the midsagittal plane.

Statistical Analysis
Continuous variables were to be expressed as mean ± standard deviation, whereas categorical variables were to be presented as frequencies and percentages.
For comparison between the case and control groups, an appropriate independent-samples statistical test was to be selected according to the distribution of the data. A p value of <0.05 was considered statistically significant, while a p value of <0.001 was considered highly significant.
For the revised sample consisting of 40 cases and 40 controls, the complete statistical analysis, including the numerical results, needs to be recalculated using the original individual-level dataset before journal submission.

Ethical Considerations
Institutional ethical approval was obtained for the original study. Written informed consent was obtained from the participants or their guardians, where applicable.

4.RESULTS
Age Distribution
The original thesis reported that the largest proportion of alcohol-dependent patients belonged to the 31–40-year age group, followed by the 41–50-year age group.
For the revised cohort of 40 cases, the exact frequency in each age group should be recalculated from the individual patient records.
Table 1. Age distribution of study participants
Table 2. Type of alcohol consumed
Table 3. MRI morphometric parameters in cases and controls
Table 4. Brain morphometric parameters according to duration of alcohol intake
Table 5. MRI manifestations of alcohol-related encephalopathies
CASES
CASE 1 – HEPATIC ENCEPHALOPATHY
Figure A – T1WI
Figure B – FLAIR
Figure C – T1WI
Figure D – T2WI
Hyperintensities are seen in the bilateral globuspallidi and bilateral cerebral peduncles on T1-weighted images, which are characteristic of hepatic encephalopathy. Mild hyperintensity is also seen in the bilateral insular cortex. These subtle areas of hyperintensity become more conspicuous on the FLAIR images. On T2-weighted imaging, subtle ill-defined hyperintensity is noted within the basal ganglia, particularly involving the caudate nucleus and putamen.
CASE 2 – MARCHIAFAVA-BIGNAMI DISEASE
Figure A – T2WI
Figure B – FLAIR
Figure C – DWI
Figure D – ADC
Symmetrical subtle hyperintensities are seen on T2-weighted and FLAIR images involving the bilateral corona radiata, crus cerebri, posterior limbs of the bilateral internal capsules and splenium of the corpus callosum.
On diffusion-weighted and ADC images, these areas demonstrate restriction. A classic “boomerang” sign is identified in the region of the splenium, where restricted diffusion is present.
CASE 3 – MARCHIAFAVA-BIGNAMI DISEASE
Figure A – FLAIR
Some of the other characteristic imaging signs described in the literature can also be appreciated in the above case.
“Ears of a Lynx” sign: A cone- or triangle-shaped T2/FLAIR hyperintensity is seen at the tips of the frontal horns of the lateral ventricles. The appearance resembles the tufts of hair at the ears of a lynx.
“Sandwich” sign: Involvement of the central layers of the splenium of the corpus callosum is seen.
CASE 4 – OSMOTIC MYELINOSIS

Figure A – T2WI
Figure B – FLAIR
Figure C – DWI
Figure D – ADC
An ill-defined area of hyperintensity is seen in the central part of the pons with relative peripheral sparing, producing the classical “trident sign” on T2-weighted and FLAIR images.
The lesion shows restriction in the form of mild hyperintensity on diffusion-weighted imaging and corresponding

hypointensity on the ADC image, consistent with pontinemyelinolysis.

5.DISCUSSION

The present study evaluates structural brain abnormalities associated with chronic alcohol use using MRI-based morphometric assessment. The major findings indicate that prolonged alcohol exposure is associated with alterations in ventricular dimensions, widening of the interhemispheric fissure, changes in brainstem measurements and abnormalities involving the corpus callosum.

The findings are in agreement with previous neuroimaging studies that have described cerebral volume loss and enlargement of the ventricular system in chronic alcohol use. Reviews of neuroimaging findings in alcohol dependence have reported cortical shrinkage and ventricular dilatation as common features. Greater involvement of selected frontal and subcortical regions has also been described among older alcohol-dependent individuals.[1]

In the original study dataset, the width of the third ventricle and the interhemispheric fissure was greater among alcohol-dependent patients compared with controls. At the same time, the anteroposterior diameter of the pons was smaller. The height and width of the fourth ventricle were also increased. Taken together, these changes are compatible with loss of cerebral and cerebellar volume.

The association between the duration of alcohol exposure and the degree of morphometric abnormality is an important finding. The source study demonstrated progressive increases in fourth ventricular dimensions with increasing duration of alcohol intake. This may indicate progressive involvement of the cerebellum and brainstem with prolonged alcohol exposure. Similar findings of ventricular enlargement and cerebellar involvement have been reported in previous MRI studies of chronic alcoholism.[4,5]

Another important observation in the study was the involvement of the corpus callosum. The source data showed a progressive reduction in the dimensions of the genu, body and splenium with increasing duration of alcohol exposure. Previous MRI studies have demonstrated that white matter is particularly vulnerable to the effects of chronic alcohol use, with abnormalities of the corpus callosum being an important manifestation.[2,3,6] More recent neuroimaging evidence has also suggested an association between patterns of alcohol consumption and structural changes involving the corpus callosum.[11]

In addition to chronic atrophic changes, the study demonstrated characteristic MRI appearances of alcohol-related neurological complications. Wernicke encephalopathy is particularly important because early recognition and treatment can prevent permanent neurological injury. MRI commonly demonstrates symmetrical involvement of the medial thalami, mammillary bodies, periaqueductal region and tectal plate.[7,8]

Marchiafava-Bignami disease is an uncommon but important neurological complication associated with chronic alcoholism and nutritional deficiency. Characteristic involvement of the corpus callosum, together with the sandwich and boomerang signs, can assist in establishing the diagnosis.[9]

Osmotic demyelination is another important condition that may occur in patients with chronic alcohol use, particularly when associated with electrolyte abnormalities. Diffusion-weighted MRI can be helpful in detecting the condition at an early stage.

Overall, the findings emphasize that MRI has a role beyond simply demonstrating chronic alcohol-related cerebral atrophy. It can also help identify specific neurological complications that may be potentially reversible or treatable when recognized early.

6.LIMITATIONS

The duration and type of alcohol consumption were based partly on the patient's history and may therefore be affected by recall bias.

Several potential confounding factors, including smoking, nutritional status, cardiovascular disease and use of other substances, may influence brain morphometry.

The study was conducted at a single institution, which may limit the generalizability of the findings.

The revised analysis involving 40 cases and 40 controls requires recalculation of all numerical results using the original individual-level dataset.

Since the study was cross-sectional in nature, it cannot provide information regarding the longitudinal progression or reversibility of the observed brain changes.

The original thesis also recognized limitations related to self-reported duration of alcohol consumption and possible confounding factors such as smoking, cardiovascular health, recreational drug use and nutritional status.

7.CONCLUSION

MRI demonstrates important structural and signal abnormalities in patients with chronic alcohol use disorder. Quantitative morphometric assessment can demonstrate enlargement of the ventricular system, widening of the interhemispheric fissure and reduction in selected measurements involving the brainstem, cerebellum and corpus callosum.

The magnitude of several of these morphometric changes appears to increase with longer duration of alcohol exposure. This supports the usefulness of quantitative MRI assessment in demonstrating structural changes associated with chronic alcohol use.

MRI is also valuable for identifying alcohol-related neurological complications. Wernicke encephalopathy, Marchiafava-Bignami disease, hepatic encephalopathy and osmotic demyelination can demonstrate characteristic imaging patterns on conventional MRI, FLAIR and diffusion-weighted sequences.

Thus, MRI provides a comprehensive and non-invasive approach for evaluating both chronic structural brain injury and acute or subacute neurological complications associated with alcohol use disorder

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