Comparative Study of Morphometric and Degenerative Changes in Brain of Alcohol Dependent Adult Male Patients in Comparison to Non Alcoholic Controls on MRI

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ABSTRACT

Background: Chronic alcohol intake leads to a myriad of morphometric and metabolic effects in brain which can be quantitatively evaluated using MRI to ascertain the effect of long term alcohol abuse. Aims and Objectives: 1.To evaluate the degenerative brain changes in alcoholic men on MRI. 2. Morphometric comparison of the results with suitable age matched controls. **Methods:** Fifty patients with alcohol use disorder established via DSM 5 Criteria and fifty age matched controls were selected and examined using MRI. The morphometric results were compared using appropriate statistical analysis tools. **Results:** Comparison of various morphometric parameters in brain of alcoholic patients showed a highly significant difference ($p<0.001$) in: 3rd ventricle width, interhemispheric fissure width, A-P diameter of pons, 4th ventricle height, 4th ventricle width, Genu, Splenium, and Body of Corpus Callosum, suggesting their pivotal role in quantitative analysis of alcoholism related cerebral atrophy. These parameters were also most altered in the group, drinking the longest s/o duration dependent atrophy of the brain. Comparative study of these parameters among sub groups divided on basis of type of alcohol consumed revealed that most significant parenchymal atrophic changes were in the subgroup of patients who consumed Desi Daru. The most commonly observed metabolic derangement in the study was hepatic encephalopathy, others were Wernicke's encephalopathy, Marchiafava Bignami and Osmotic Myelinosis. **Conclusion:** Significant variations in the morphometric parameters of various white and grey matter structures of brain were seen in the alcoholic and non alcoholic group which can be proven quantitatively using MRI.

Keywords: MRI in chronic alcoholism, morphometric study in alcoholics, hepatic encephalopathy Wernicke's encephalopathy, Marchiafava Bignami, Osmotic Myelinosis.

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INTRODUCTION

Alcohol is an organic solvent especially known for its use for human consumption. The type of alcohol that is found in alcohol beverages is ethanol. Most common alcohol beverages are beer, wines, and spirits. Alcohol has been known to mankind for its intoxicating effects since ancient times. The risk for several disorders, including liver cirrhosis, cardiovascular disease, multiple forms of cancer, and neuropsychiatric conditions, increases as a result of alcohol use. Another negative effect of alcohol is its addictive potential. When comparing the adverse effects of alcohol with those caused by other drugs of abuse, categorized as hard drugs, one could argue that alcohol should be classified as a hard drug. Yet, most government laws consider alcohol as legal under certain minimum age restrictions.[1]

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According to a study done at Chandigarh by Chavan et al, Alcohol was the primary substance of dependence for majority of urban slum substance users and rural area users.[2] Another study by Singh et al done at Amritsar showed that regular alcohol users were in the order of 10.8 and 17.0 percent in urban and rural area respectively.[3]

Alcohol is known to cause a myriad of health problems and amongst all the complications associated with alcohol use, its effects on the Central Nervous System seem to be the most significant. There are a number of ways in which alcohol (ethanol) is thought to impact the central nervous system: direct neurotoxicity, toxicity of metabolic by-products (e.g., acetaldehyde) and effects of secondary nutritional states and chronic liver disease.[4]

Chronic ethanol intoxication may lead to atrophy related to loss of subcortical white matter and lacerations in the number and size of neurons. Associated malnutrition can cause Wernicke encephalopathy, which is due to thiamine deficiency. Marchiafava Bignami disease, characterized by acute demyelination of the corpus callosum can also occur. Hepatic Encephalopathy is a potentially reversible syndrome occurring during the acute and chronic liver failure that is associated with deposition of neurotoxic substance in the CNS.[5]

Magnetic resonance imaging (MRI) has become the method of choice for the examination of macroscopic neuroanatomy in vivo due to excellent levels of image resolution and tissue contrast.

MRI has several advantages such as no ionizing radiation, higher tissue characterization, and lesser chance of causing allergic reaction by contrast agent and is more sensitive and specific for abnormalities within the brain.[6]

Areas of the brain that are especially vulnerable to alcoholism–related damage are the cerebral cortex and subcortical areas such as the limbic system (important for feeling and expressing emotions), the thalamus (important for communication within the brain), the hypothalamus (which releases hormones in response to stress and other stimuli and is involved in basic behavioral and physiological functions), and the basal forebrain (the lower area of the front part of the brain, involved in learning and memory) (Oscar–Berman 2000).[7] Besides the various morphological changes and volume loss occurring as a long term effect of alcoholism, a number of metabolic disturbances which are acute and subacute in nature have also been studied and account for a significant amount of morbidity related to chronic alcoholism. These include conditions like Wernicke's encephalopathy, Marchifava Bignami disease, osmotic pontine demyelination and hepatic encephalopathy.

Wernicke's encephalopathy (WE):

Wernicke's encephalopathy is an acute neuropsychiatric disorder resulting from thiamine (vitamin B1) deficiency and characterized by a clinical triad of confusion, ocular abnormalities, and ataxia.

The most distinctive neuroimaging finding of acute WE are cytotoxic edema and vasogenic edema, which are represented by bilateral symmetric hyperintensity alterations on T2-weighted MRI images in the periphery of the third ventricle, periaqueductal area, mammillary bodies and midbrain tectal plate. These areas show hyperintensity on FLAIR and demonstrate contrast enhancement suggestive of areas off vasogenic edema.[8]

Marchifava Bignami Disease:

Marchiafava-Bignami disease (MBD) is characterized by the demyelination and necrosis of the corpus callosum and may involve the adjacent subcortical white matter.[9]

In the acute stage, cytotoxic edema dominates. MRI may reveal hypointense T1 signal, hyperintense T2/Fluid-attenuated inversion recovery (FLAIR) signal in middle layer of the corpus callosum (sandwich sign), diffusion restriction on DW sequence, and/or variable reduction in apparent diffusion coefficient (ADC) sequence.[10] Another signal that can be observed is hyperintensity involving the entire splenium ("Boomerang sign").[1] Although the callosal lesions have been described as the hallmark of this disease, few cases of MBD also demonstrate signal intensity abnormalities in frontal lateral and temporal cortices (Morels cortical laminar sclerosis).[12]

Osmotic Pontine Demyelination:

Osmotic Demyelination Syndrome (ODS) includes Central Pontine Myelinolysis (CPM) and Extrapontine Myelinolysis (EPM). This condition has been described in cases of chronic Alcohol Dependence Syndrome and in rapid correction of hyponatremia.

On CT, ODS typically manifests as low-density lesions in the pons or other affected regions, and occasionally shows enhancement. In acute CPM, MRI shows signal alteration in the central pons with sparing of the tegmentum, ventrolateral pons and corticospinal tracts. On DWI, mildly restricted lesions can be detected within 24 hours after onset of symptoms and thus provide the earliest indication of this disease entity.[13]

Hepatic Encephalopathy:

Hepatic encephalopathy (HE) is a functional and potentially reversible syndrome occurring during acute and chronic liver failure or after portosystemic shunt surgery.

The chronic phase is characterized by symmetric T1 high-signal-intensity alterations in the basal ganglia (more often the globus pallidus), the subthalamic nucleus, mesencephalus, tectal plate, hypothalamus, and adenohypophysis. The described T1 hyperintensity is caused by deposition of manganese, which is alleviated on normalization of liver function.[14]

Aims and Objectives

1. To evaluate the role of MRI in detecting degenerative brain changes in alcoholic men.
2. To compare the results with suitable age matched controls

MATERIALS & METHODS

The study was conducted in the Department of Radiodiagnosis, Guru Nanak Dev Hospital attached Govt. Medical College, Amritsar, Punjab from June 2017 to November 2019 with permission from the institutional ethics committee Govt. Medical College Amritsar.

Fifty patients with alcohol use disorder established via DSM 5 Criteria were included in the study and fifty age matched controls were selected. The study was conducted after taking written informed consent from them/ guardian.

Inclusion criteria:

- Patients with AUD in the age group 21-60 years.
- Patients meeting the DSM 5 criteria

Exclusion Criteria:

- Patients > 60 years of age
- Traumatic injury
- Patients with:
  - Epilepsy
  - Delirium tremens
  - Dementia
  - Any organic or psychiatric disorder
  - Patients suffering from claustrophobia

Imaging Technique:

MRI imaging was done with 1.5 Tesla Siemens Magetom machine and following sequences were selected as required

- Midline sagittal plane with a field echo pulse sequence or with a spin echo sequence
- Axial T2 weighted sequence
- Axial T1 weighted spin echo sequence
- Coronal T1W and T2W sequence
- FLAIR sequence
- ADC mapping

Duration of Study: 3 years

Ethical clearance was obtained from the Research and Dissertation Committee/ Ethical Committee of the institution for this study.

RESULTS

Table 1: Age of Cases

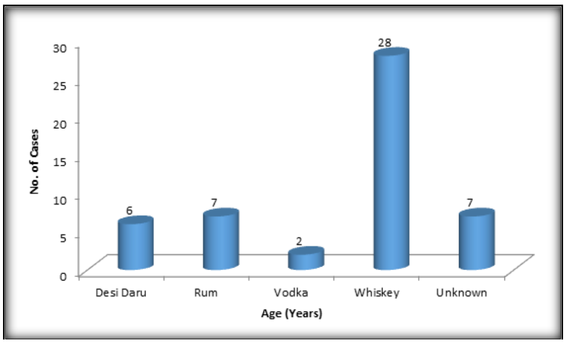
AGE (years)	Cases	Percentage
21-30	9	18.0
31-40	16	32.0
41-50	15	30.0
51-60	10	20.0
Total	50	100.0

[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 2: Type of Alcohol Consumed

Type of Alcohol	No. of Patients	Percentage
Desi Daru	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 & 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 Desi Daru. 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%).



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 3: 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

Table 4: 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>0.05NS
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>0.05NS
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>0.05NS
cerebellar vertical length	40.55±4.21	40.67±3.41	p>0.05NS
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**

Table 5: 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

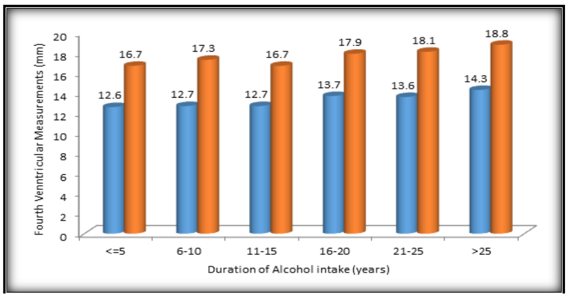
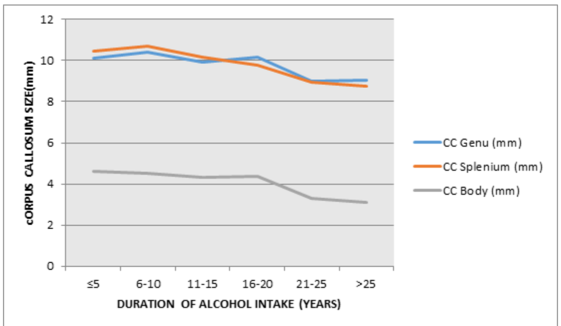


Table 6: Corpus Callosum Size In Relation to the Duration of Alcohol Intake

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

Here we see the relationship of 4th 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 4th ventricle height and width suggesting that there was a proportional reduction in the size of cerebellum and the brainstem volume.

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

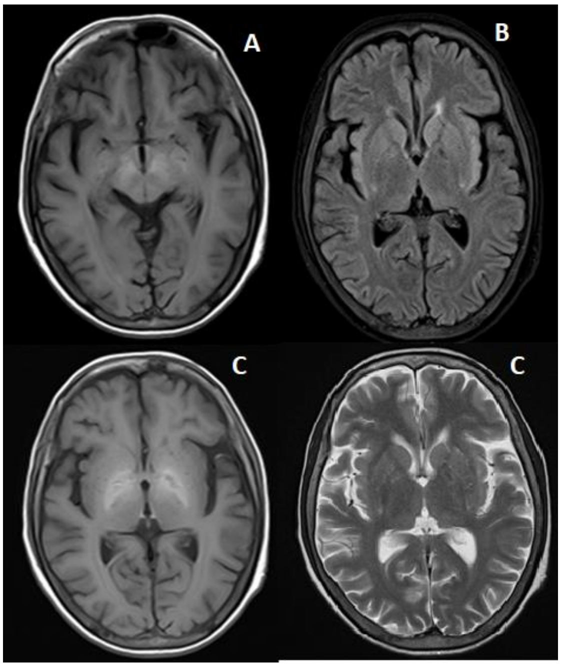


Figure1: (A): T1WI, (B): FLAIR, (C): T1WI, (D): T2WI.

Hyperintensities are seen within B/L Globus Pallidi and B/L cerebral perdunce 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

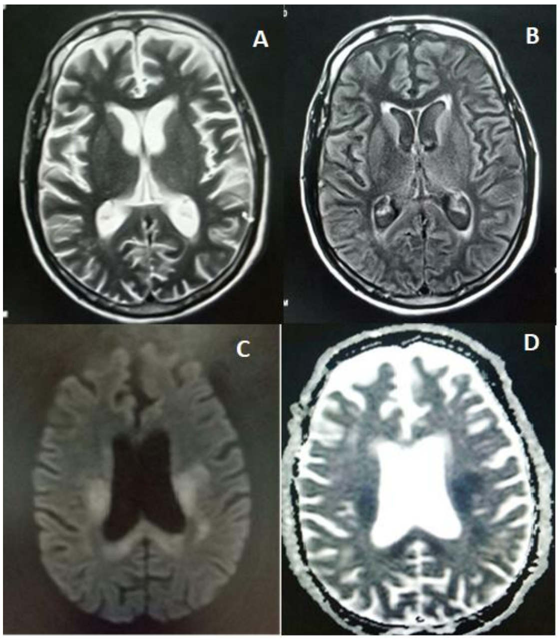


Figure 2: (A): T2WI, (B): FLAIR, (C): DWI, (D): ADC

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

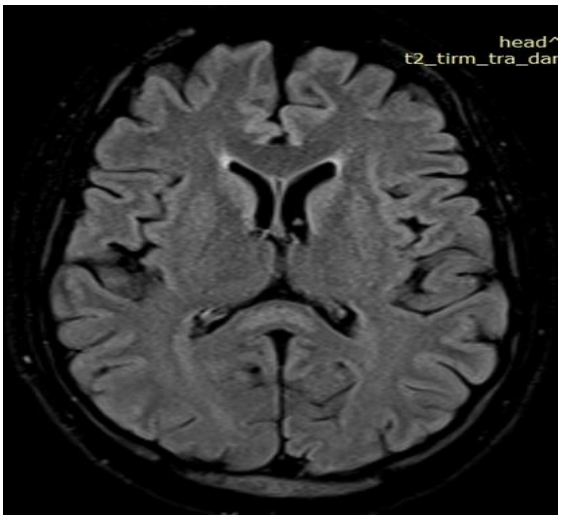


Figure 3: FLAIR

Some other classic signs described in the literature can be seen in the case shown above.

1. "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
2. "Sandwich Sign" - Involvement of the central layers of splenium of the Corpus Callosum.

Case 4 - Osmotic Myelinosis

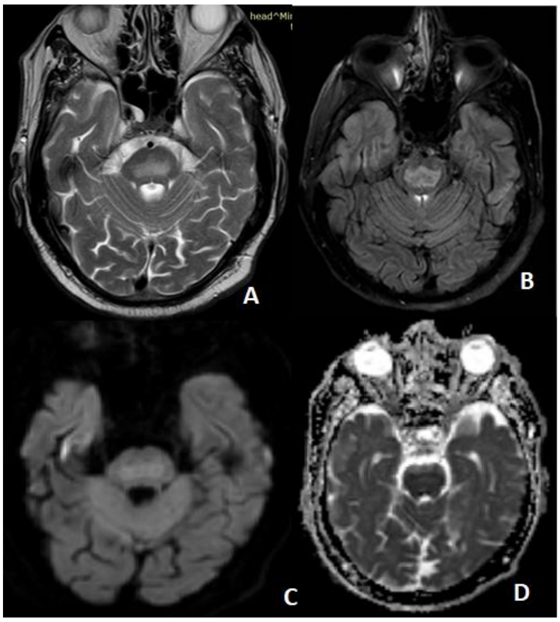


Figure 3: (A): T2WI, (B): FLAIR, (C): DWI, (D): ADC

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

DISCUSSION

The present study was undertaken to evaluate and describe the various degenerative changes and morphometric variations in brains of adult male patients suffering from alcohol dependence and their comparison to non-alcoholic controls.

We evaluated 100 patients, out of which 50 had history of alcoholism and 50 patients with no such history were evaluated as controls and compared together on the basis of various findings and specific spatial measurements on MR imaging. Appropriate statistical analysis was done.

Quantitative assessment of alcohol related atrophy of various supratentorial and infratentorial structures was done. Measurement of the various brain regions was performed with sliding calipers.

Width of the 3rd ventricle and the interhemispheric fissure was the highest in the patients with highest duration of drinking. The mean 3rd ventricle width in the group drinking for about 25 years was 8.20mm +/- 0.42 whereas in those drinking for about 6-10 years was 7.37mm +/- 0.84. This finding is suggestive of dilatation of the 3rd ventricle proportional to the number of years of alcoholism. These findings imply that as the number of years of drinking increases, the amount of atrophy of the brain parenchyma increases.

The morphometric measurements acquired were compared between the cases and the controls. All data was expressed as the mean and standard deviation. For statistical analysis, Student's t-test was used and $p < 0.05$ was considered significant (S) and $p < 0.001$ was considered highly significant.

The mean value of A-P diameter of Pons in the alcoholic patients was 22.79mm +/- 3.89 as opposed to 25.06mm +/-1.79 in the non-alcoholic subjects. The p value in this case was found to be <0.001 suggesting it to be a highly significant difference between the two groups.

The mean height and width of IV ventricle was found to be approximately 14.3mm +/- 0.57 & 18.8mm +/- 0.21 respectively in the group with a history of more than 25 years of alcohol intake whereas, among those with a history of less than 5 years was 12.6mm +/- 1.18 & 16.7mm +/- 0.55 respectively. We infer that as the duration of alcohol intake increased, there was an increase in the 4th ventricle height and width suggesting that there was a proportional reduction in the size of cerebellum and the brainstem volume, leading to 4th ventricle dilatation over time.

A-P diameter of pons was the highest in the subgroup of patients who consumed Rum (24.5mm +/- 2.69) whereas it was lowest in the subgroup taking whisky and desi daru (22.2mm +/- 4.49 and 21mm +/- 3.21 respectively).

The mean 3rd ventricle width in patients consuming Vodka and Rum was 6.9mm +/- 0.92 and 7.4mm +/- 1.05 respectively on the other hand, in Desi daru consumers it was found to be 8.3mm +/- 0.61.

The size of the ventricles increases as the duration of the alcohol intake grows. The mean 3rd ventricle width in people with 11 to 15 years of alcohol consumption is 7.37mm +/- 1.23 which increases to about 8.2mm +/- 0.42 in people with more than 25 years of alcohol intake. Similarly the 4th ventricle width was 16.7mm +/- 1.72 in cases with 11 to 15 years and 18.75mm +/- 0.21 in cases with more than 25 years of alcohol intake. It can be deduced that the ventricular size does not grow considerably until 15 years of liquor intake. But after 15 years, there is a striking increase in the ventricular size suggesting that it takes a significant amount of time before there is morphological evidence of brain atrophy.

The brain measurements revealed significant cerebral atrophy (characterized by lateral and 3rd ventricular dilatation, and widening of the interhemispheric fissure) as well as significant cerebellar atrophy (represented by 4th ventricular dilatation) in the alcoholic group. These changes were more prominent in patients in with more than 20 years of alcohol intake as compared to those with lesser years of alcohol dependence.

These observations suggest that alcohol is an important promoter of brain atrophy and certain areas are more affected than the others.

Out of the 50 cases that were examined in our study, metabolic findings were found in 15 cases. 6 cases showed findings suggestive of hepatic encephalopathy, 4 cases of Wernicke's encephalopathy were seen. There were 3 cases with findings consistent with Marchiafava Bignami disease and 2 cases of Osmotic Myelinosis were seen.

CONCLUSION

100 male patients, 50 of which presented with history of alcoholism and 50 controls with no history of alcohol intake, referred from the wards and outpatient departments of Guru Nanak Dev Hospital attached to Government Medical college, Amritsar to the department of Radiodiagnosis were included in the study.

All the cases & controls included in the study underwent brain scan with a 1.5T seimens MRI machine after written informed consent. The appropriate brain morphometric measurements were taken, data and results were collected, assimilated and statistical analysis was performed and valid conclusions were drawn.

1. The age range of patients was found to be from 21 to 60 years with maximum number of cases of alcoholism was observed in the age group of 31 to 40 years (32%) followed by 41 to 50 years (30%)
2. The type of alcohol consumed by maximum number of patients in the study was Whiskey (56%) followed by Rum (14%) and Desi Daru (12%). The type of alcohol could not be determined in 14% of patients due to unreliable history and poor recollection.
3. 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, Splenium, and Body of Corpus Callosum.
4. 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.
5. There was slight decrease in the white matter volume in Corpus Callosum genu, body and splenium size as the extent of alcohol intake gradually increased. After 20 Years of alcohol intake, the CC Genu size decreased by approximately 12%. The Body and the Splenium size decreased by approximately 27% and 13.8% respectively

6. Cases of Marchifava Bignami disease showed symmetric subtle T2 and FLAIR hyperintensities involving bilateral corona radiata, crus cerebri, posterior limb of B/L internal capsule and splenium of corpus callosum. Classic "Boomerang" sign can be seen in the region of the splenium. The "Ears of a Lynx Sign" that is T2/FLAIR cone (triangle) shaped hyperintensity at the tip of the frontal horn of the lateral ventricles and the "Sandwich Sign" which is involvement of the central layers of splenium of the Corpus Callosum were also seen in one case.
7. Both cases of Pontine myelinosis showed Ill defined areas of T2/FLAIR hyperintensity in the central part of pons with peripheral sparing demonstrating the classical "Trident Sign" along with diffusion restriction on DWI and hypointensity on ADC.

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