Original Article

Study to Find Out the Correlation Between Cognitive Defect and Non-alcoholic Fatty Liver Disease

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Introduction : Non-alcoholic Fatty Liver Disease (NAFLD), a hepatic manifestation of Metabolic Syndrome, has now become a Global Phenomenon and along with its increasing prevalence various morbidities and mortality are also increasing.

Aims and Objectives : The objective of the present study was to establish whether patients with NAFLD, in the absence of other comorbid conditions suffer from cognitive impairment.

Materials and Methods : This cross sectional study was conducted at the Department of General Medicine, Calcutta National Medical College and Hospital. 90 patients with NAFLD and 90 healthy controls were recruited after matching all the inclusion and exclusion criteria, from the out patient and in patient department over a period of 1 year starting March, 2019. NAFLD was diagnosed by noninvasive methods including Elastography (fibroscan). Cognition was assessed by MoCA (Montreal Cognitive Assessment test) score.

Result : The mean age of cases and control were 49.2 and 48.5 years, respectively. Out of total cases and controls 48.9% was male and 51.1% was female. The mean BMI of the cases and control were 30.21±4.24 and 22.60±1.52 Kg/m2, respectively. The mean Elastography score among the cases was 4.91±0.23 kPa and that among the controls was 3.84±0.31 kPa. The mean Fibroscan Score among male cases and controls were 4.907±0.26 kPa and 3.83±0.35, respectively ($p<0.05$). In case of females, Fibroscan Score was 4.906±0.21 for cases and 3.85±0.29 for controls. After the groups were matched for age and gender, we found that 33.3% of the cases had a MoCA score < 26, whereas only 6.7% of the control population showed similar results. The mean score among the cases was 26.24±1.58 which was significantly less than that found in the control population (28.89±1.2). The patients with normal BMI with cognitive defect had a mean MoCA score of 23.80±1.5 and those without cognitive defect had a mean MoCA score of 29.13±1.1. The difference between the two groups was statistically significant.

Conclusion : A statistically significant cognitive difference was found between the two groups (NAFLD *versus* controls), with a higher cognitive deficit recorded among patients with NAFLD. Percentage of people with Cognitive defect appears to be greater among the NAFLD patients even after they were matched for Body Mass Index (BMI).

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Key words **: Fibroscan, MoCA, BMI.**

The prevalence of Non-alcoholic Fatty Liver Disease (NAFLD) is constantly increasing (15% in 2005 to 25% in 2010) with a Global Prevalence of 25.24% currently[1].

The stages of NAFLD are Fatty Liver (steatosis), Non-alcoholic Steatohepatitis, Fibrosis and Cirrhosis.

NAFLD is now recognized as the Hepatic manifestation of Metabolic Syndrome[2]. Obesity has the strongest association with NAFLD. While 30% of patients who are obese have Fatty Liver, up to 80% of morbidly obese patients (BMI > 35) have NAFLD[3].

Noninvasive studies like Ultrasonography, Computed Tomography Scanning and Magnetic Resonance Imaging (MRI) and MR Elastography are useful tools to establish a diagnosis of Steatosis[4], complementing blood tests. Studies show that Ultrasonographic diagnosis of Steatosis of any degree was seen to be 60.9% sensitive and 100% specific.

Liver stiffness measured by transient Elastography [recorded in kilopascals (kpa)] have demonstrated diagnostic accuracy for assessing Fibrosis[5]. Transient Elastography is a remarkable alternative to Liver Biopsy, which, being an invasive procedure is garnering

Editor's Comment :

- NAFLD is a fast emerging and vastly prevalent disease. While it's negative implications are far reaching, not only by it's impact on General Health, but also it's ability to cause cognitive defect, awareness regarding the same and early intervention can help stall the disease process.

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reluctance with most patients, especially Asymptomatic ones.

Our study aims to correlate cognitive defect with NAFLD. 'Cognition' means "thinking and awareness". MoCA (Montreal Cognitive Assessment test) is a test of cognitive function, testing 7 separate domains and is multiple languages accessible. It is a 30-point test administered over 10 minutes. The sensitivity and specificity of MoCA for detection of MCI (Minimum Cognitive Impairment) was found to be 90% and 87% respectively, compared with 18% and 100% respectively for the MMSE[6].

Various studies have proven that a correlation exists between NAFLD and CNS manifestations like Depression, Dementia, etc. Our study aims to substantiate the same, eliminating other risk factors.

Aims and Objectives

The objective of the present study was to establish whether patients with NAFLD, in the absence of other comorbid conditions suffer from cognitive impairment.

Materials and Methods

This cross-sectional study was conducted at the Department of General Medicine, Calcutta National Medical College and Hospital in collaboration with the Ultrasound Unit of the same Department. 90 patients with NAFLD and 90 healthy controls were recruited from the Outpatient and Inpatient Department over a period of 1 year starting March, 2019.

Inclusion Criteria :

Patients aged 18-60 years with NAFLD.

Controls- patients of the same age group without any comorbidities.

For defining NAFLD, there must be (1) evidence of Hepatic Steatosis (HS), either by imaging or histology, and (2) lack of secondary causes of Hepatic Fat accumulation[7].

We have diagnosed our patients based on Ultrasonography and Fibroscan which is sufficient for diagnosis.

Cognitive assessment was done using the MoCA scale. A score <26 out of 30 was taken as evidence of cognitive defect[8].

Exclusion Criteria :

- Previous history of Hepatitis, Cirrhosis, or other Chronic liver disease, Autoimmune hepatitis, Haemochromatosis
- Presence of severe Cardiopulmonary disease
- Obstructive Sleep Apnoea Syndrome
- Endocrinological disorders: Hypothyroidism, Hypercorticism, Syndrome of the polycystic ovaries
- History or Clinical signs of excessive Alcohol abuse (>20 g/day for males and >10 g/day for females)
- Visible focal or diffuse changes in the grey matter of the brain on MRI.
- Fazekas score more than 0 on MRI scan
- Rheumatological disease
- Psychiatric disease and/or Psychiatric medication history or Hepatotoxic drugs
- Traces of illicit drugs abuse: positive urine multiple drug tests.
- Use of antidiabetic drugs, insulin, antilipemic drugs, uricosuric drugs, steroids and oral contraceptives.
- Advanced Liver Disease with Hepatic Encephalopathy

The data obtained from the above study was analyzed by standard statistical methods using SPSS v.20.

Descriptive statistical analysis was performed to calculate the means with corresponding Standard Deviations (SD). Test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference proportions and Chi-square ($\chi 2$) test was performed to find the associations.

t-test was used to compare the means of the two groups. Fisher Exact test was used where Chi-square ($\chi 2$) test was not applicable. $p<0.05$ was taken to be statistically significant.

Results

We recruited 90 NAFLD patients (cases) and 90 controls aged between 18 and 60 years. The mean age of cases and control were 49.2 and 48.5 years, respectively. Percentage of male and female patients was 48.9% and 51.1%, respectively in total groups.

The mean weight (kg) in study population was found to be 83.27 ± 10.87 which was more than the control group (60.93 ± 7.65).86.7% of the cases and 6.7% of the controls were found to have a BMI above 24.9. The mean BMI of the cases and control were 30.21 ± 4.24 and 22.60 ± 1.52 Kg/m^2, respectively.47.8% of males had a waist :hip ratio $\geq$ 0.9 among cases and 33.3 % of the females had a ratio > 0.85; in comparison, 3.3% of males and 7.8% of females in the control group had a ratio > 0.9 and 0.85 respectively.The mean waist hip ratio among cases was 0.99±0.16 and among the controls was 0.83±0.04 which is statistically significant.

NAFLD group, 10 out of 44 male patients had an abdominal girth >102 cm (11.1%), while none of the male controls fell in the same category. 28 out of 46 female cases had an abdominal girth >88cm (31.1%) and 1.1% of the controls (1 female) showed similar

results. The mean abdominal girth for cases was 94.32 ± 6.92 cm and that of control population was 81.23 ± 4.48 cm, which was significantly different.

In our study 77.8% of cases and 24.4% of controls had a liver span >155mm (normal <155mm). The mean liver size among cases was 156.12 ± 1.65 and 152.94 ± 2.19 among controls, which was significant.96.7% of the cases and 100% of the control patients had a spleen size less than 125 cm (normal average).

95.6% of patients with NAFLD had an AST > 35 IU/L as compared to only 10% of control patients. The mean Aspartate Transaminase (AST) of cases and control were 46.77 ± 6.94 and 28.11 ± 4.88 which was significant. 98.9% of cases had an ALT of 40 IU/L as compared to only 7.8% of the control patients. The mean Alanine Transaminase (ALT) of the cases group was 58.10 ± 8.21 and that of the control population was 32.58 ± 5.01 which was significant.

The Gamma-glutamyl Transferase (GGT) levels of all patients who participated in the study was <60U/L.

81.1% of cases and 98.9% of controls had a Total Bilirubin value within normal range of 0.8 to 1.2 mg/dl.

All the cases and 98.9% of the controls had a Total Protein (TP) value within the normal range. The mean difference was 0.15 and was not significant.

The ideal Fibroscan values for a normal Liver without any insult or scarring are between 2-5.7 kPa. In our study 98.9% of the cases and all controls had a normal score. The mean score among the cases was 4.91 ± 0.23 and that among the controls was 3.84 ± 0.31.

The mean Fibroscan value among the male and female cases were 4.907±0.26 and 4.906±0.21, respectively, signifying no difference.

The mean Fibroscan score among male cases and controls were 4.907±0.26 and 3.83±0.35, respectively ($p<0.05$). The mean Fibroscan score among female cases and control were 4.906±0.21 and 3.85±0.29, respectively. Mean difference was 1.056 and statistically significant.

Further, the mean Fibroscan values were seen to be higher in patients who were older: 4.50±0.1 among the NAFLD patients in 21-30 age group *versus* 4.96±0.3 in the 51-60 group.

The NAFLD patients were divided based on gender among the different age groups and Fibroscan values compared. There was no statistically significant difference among Fibroscan Scores between male and female cases when distributed among different age groups.

After the groups were matched for age and gender, we found that 33.3% of the cases had a MoCA score <26, whereas only 6.7% of the control population showed similar results. The mean score among the cases was 26.24 ± 1.58 which was significantly less than that found in the control population (28.89 ± 1.2).

84 out of total 180 persons had a high BMI, whereas 96 had a normal BMI.

Among whole study population (irrespective of NAFLD),30.9% ofpersons with a BMI =25 Kg/m2 had a MoCA score <26; whereas, 89.6% of the persons with a normal BMI had a normal Cognitive Score (≥26)(Fig 1).

The patients with high BMI with cognitive defect had a mean MoCA score of 24.04 ± 1.3, those without cognitive defect among the above group had a mean MoCA score of 27.48 ± 1.2 (Fig 2).

The patients with normal BMI with cognitive defect had a mean MoCA score of 23.80 ± 1.5, and those without cognitive defect had a mean MoCA score of 29.13±1.1. The difference between the two groups was statistically significant.

Further, 25 out of 78 NAFLD (32.2%) cases with high BMI had Cognitive score <26 and only one out of 6 controls with high BMI had a Cognitive Score <26 (16.7%). Five out of 12 NAFLD cases with normal BMI had a Cognitive Score <26 (41.7%). Five out of 84 controls with a normal BMI had a Cognitive score <26 (5.9%).The mean Cognitive score among the NAFLD

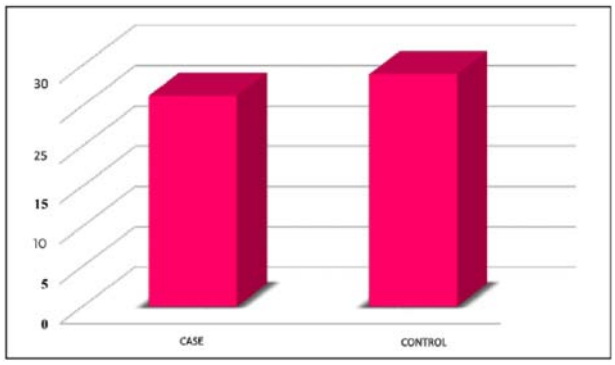

Fig 1 — Comparison of mean Cognitive Score of the patients between the two groups

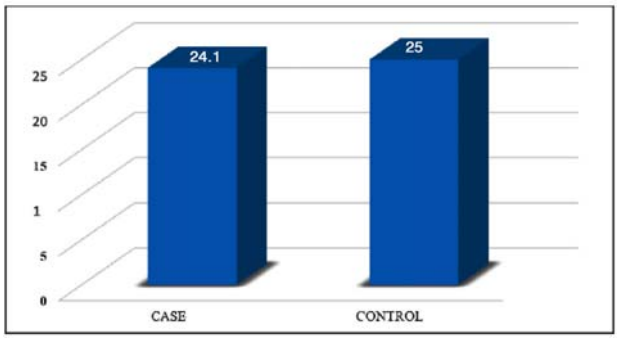

Fig 2 — Comparison of mean Cognitive defect of the patients with BMI>25 kg/m2 of the two groups

patients with a normal BMI was 24.0±0.7 and among controls was 23.6±2.1. The difference of the mean cognitive defect between these two groups is however, not statistically significant (P>0.05).

Discussion

The results of our study show that there is a definite correlation between NAFLD and Cognitive Defect (diagnosed using the Montreal Cognitive Assessment scale). The cases showed a greater decline in cognitive function along with higher BMI, Waist Hip Ratio, Triglyceride and Total Cholesterol levels. Thus, various parameters of Metabolic Syndrome appear to be intricately involved in causing NAFLD and further, a decline in cognition as has also been proved in studies by Sang Won Seo, Rebecca F Gottesman, Jeanne M Clark, *et al*[9].

The Pathophysiology behind the relation between these risk factors and Cognitive deficit though still elusive, is a much explored and debated prospect and various studies are attempting to prove and explain the same. While the degree of Cognitive defect was significantly higher in the NAFLD patients most of whom had a higher BMI, it was surprisingly enough seen that the percentage of Cognitive defect was greater among the NAFLD patients even after they were matched for BMI.

Most studies correlating NAFLD and Metabolic Syndrome have shown a direct relation to NAFLD and cognitive defect with Diabetes[10]. Our study is different in that we excluded Diabetes; and NAFLD without Diabetes was independently associated with a decline in Cognitive function. Further studies are required in this field to achieve more clarity.

Finding an association between NAFLD with cognitive defect as shown in this study can help in early intervention and more intensive management to try to stall, if possible, halt, further progression of the disease.

Ascertaining the validity of these non-invasive measures in diagnosing NAFLD and in prediction of further disease course including progression of cognitive deficit can however be achieved only with a longer study duration, a much larger study population, and more stringent follow up of patients. A greater recruitment into both groups with equal representation of patients with high and low BMI can provide unbiased clarity when studying the repercussions of NAFLD on Cognitive defect.

Conclusion

Our study, to find out the correlation between NAFLD and Cognitive defect is possibly the first such study conducted in East India. A statistically significant Cognitive Difference was found between the two groups (NAFLD *versus* controls), with a higher Cognitive Deficit recorded among patients with NAFLD.

Percentage of people with Cognitive defect appears to be greater among the NAFLD patients even after they were matched for BMI.

BMI, however, appears to be an important confounding factor with respect to cognitive defect as our study was not confidently able to rule out the above to satisfaction.

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Conflict of Interest : None

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