

Blood thiamine levels correlate with Mammillary body volume in acute and acute-on-chronic liver failure patients of non-alcoholic etiology

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Introduction: Mammillary body (MB) atrophy in alcoholic liver disease is presumed to be due to thiamine deficiency. Liver is the principal storage site for thiamine and stores 2.0 to 7.6mg/g compared to 1.0 to 4.1mg/g in the brain and 2.8–7.9mg/g in the heart (1). The most common cause of thiamine deficiency is its poor intake in the food and/or reduced absorption in the small intestine, others include alcohol abuse, crash dieting and renal dialysis. It has been reported that thiamine storage may be reduced in patients with acute alcoholic liver disease (2), non-alcoholic liver disease, such as impaired metabolism, storage, decreased liver cell mass, along with decreased intake and poor absorption that results from chronic congestion in the mesenteric venous system (3). It leads to specific brain lesions, generally attributed to decreased levels of thiamine diphosphate, an essential cofactor in energy metabolism (4). MBs and fornix volume are reduced in conditions such as obstructive sleep apnea, Alzheimer's disease (5,6). MBs receive fibers from the hippocampus via the fornix, send efferents to the anterior and dorsal thalamus (7), and are essential to route signals between brain areas that integrate memory information. The purpose of this study was to explore the relationship among blood thiamine, MBs, major fiber bundle fractional anisotropy, and volume changes with diffusion tensor tractography (DTT) in patients with acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) of non-alcoholic etiology.

Materials and methods

Subjects: Ten patients with ALF and 11 of ACLF with non-alcoholic etiology in different grades of encephalopathy with 16age/sex matched healthy controls were included in this study. Seven patients of ALF who recovered from hepatic encephalopathy were studied after 5weeks of therapy. Mental state examination was performed and hepatic encephalopathy, if present, was graded according to West Haven criteria. Routine clinical serology was performed in all these subjects. Blood thiamine was measured from the serum of patients as well as controls (8).

Data acquisition: All the patients underwent conventional MRI and DTI on a 3T MR scanner by using 8 channel head coil after the approval from the institutional ethics committee. The diffusion tensor encoding used was a vender supplied DTI scheme with 10 uniformly distributed directions. DTI was performed in the axial plane and had identical geometrical parameters: The diffusion weighting b-factor was set to 1000 s/mm² field of view (FOV)=240×240 mm², slice thickness=3mm, interslice gap=0 and number of slices=46. For the quantification of MBs volume, 3D Fast Spoiled Gradient Echo Brain Volume with following parameters: 1mm thickness with TR=7.8ms and TE=3.0ms, inversion time 400ms, number of averages 1, image matrix of 512×512 with flip angle 13 was performed. The algorithm and detailed methodology used in DTT are described elsewhere (9). Volume of major fiber bundles was measured from the fibers obtained using above method.

Statistical analysis: Independent samples T-test was performed to look whether any blood thiamine level, MBs volume and FA value of fornix fiber between patients and controls. Bivariate correlation was also performed between MBs and fornix volume and blood thiamine level of these patients. Paired 't' test was performed to compare changes in blood thiamine levels, MBs volume and FA as well as volume of major white matter fiber bundles between the baseline and follow up study.

Results: Significant decrease in blood thiamine levels was noted in patients with ALF[(42.8±7.4nmol/L),p=0.001] and ACLF[(49.2±13.6nmol/L),p=0.001] as compared to healthy controls (81.9±10.2nmol/L). ALF group showed relatively more decrease in blood thiamine levels as compared to ACLF but this difference was not statistically significant (p=0.55) (fig.1). Significantly increased blood thiamine levels were noted in ALF patients after 5 weeks of clinical recovery [(73.4±2.5nmol/L) as compared to baseline (46.1±5.1nmol/L),p=0.001]. Significant decrease in left and right MBs volume was noted in patients with ALF(right=0.25±0.06mm³,p=0.001;left=0.21±0.05mm³,p=0.001) and ACLF(right=0.32±0.08mm³,p=0.008; left=0.31±0.07mm³,p=0.001) as compared to controls (right=0.45±0.01mm³;left=0.44±0.08mm³) (fig.2). On following up ALF patients, significant recovery was noted in right(0.36±0.07mm³,p<0.03) and left(0.33±0.05mm³,p=0.008) MBs volume, compared to baseline values (0.27±0.05mm³ & 0.23±0.06mm³ respectively). Patients with both ALF(0.30±0.01,p=0.002) and ACLF(0.30±0.02,p=0.015) had significantly decreased fornix fiber bundle FA values as compared to controls (0.32±0.02) (fig.3). Significant decrease in fornix fiber bundle volume was noted in patients with ALF(2145.1±385.26 mm³,p=0.01) and ACLF(2107.7±640.07mm³,p=0.02), as compared to controls (2863.2±651.3mm³) (fig.3). In both ALF and ACLF patient groups, blood thiamine levels showed positive correlation with MBs volume(p=0.01,r=0.80) and fornix fiber bundle volume(p=0.08,r=0.36). Blood thiamine level showed strong correlation with MBs volume while it did not correlate significantly with fornix volume (fig.3 A&B).

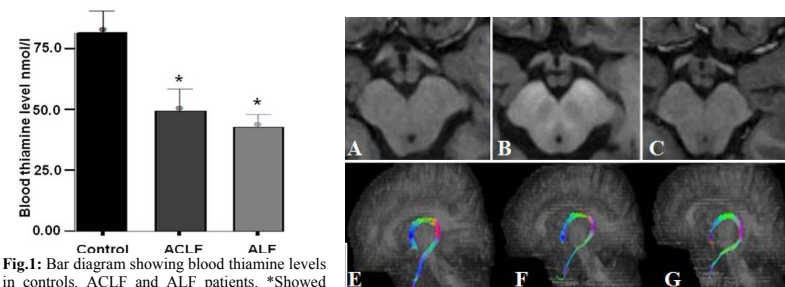


Fig.1: Bar diagram showing blood thiamine levels in controls, ACLF and ALF patients. *Showed significant difference as compared to controls.

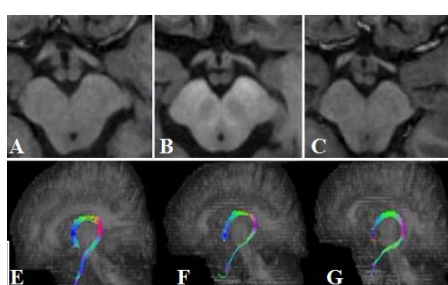


Fig.2: Image showing the MBs size in control (A), ACLF (B) and ALF (C) patient. MBs size appeared reduced in patient groups as compared to control. Fornix fiber bundle in healthy control (E), baseline (F) and in post recovery (G) in ALF patients.

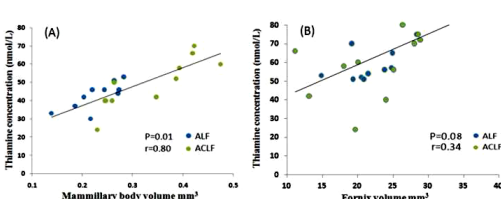


Fig.3: Scattered plot showing correlation of blood thiamine levels with MBs (A) and fornix volume (B) in patient of acute-on-chronic liver failure and acute liver failure.

Discussion: Significantly decreased blood thiamine level in these patients is probably due to the acute liver dysfunction, massive necrosis of liver and reduced storage. Thiamine is a key component in various metabolic pathways i.e. Kreb's cycle and Pantose monophosphate shunt. In the presence of thiamine deficiency, these cellular systems begin to fail, with resultant energy failure eventually leading to cell death (10). It is well established that MBs are pathologically small in a number of neurological disorders such as WE, mesial temporal sclerosis, infarction, and Alzheimer's disease (5,11). D'Aprile et al had reported the rapid shrinkage of MBs in only 2weeks by sequential MRI studies in acute WE (12). In our study, an average duration of illness at the time of performing MR studies was 14 days in ALF and 26days in ACLF. This rapid shrinkage of MBs observed in patients with ALF and ACLF can be explained on the basis of poor liver function due to massive necrosis of liver cell mass with near or complete loss of thiamine storage associated with poor intake, resulting in a state of acute thiamine deficiency. We observed significant reduction in FA values along with fornix volume in these patients which did not recover even when blood thiamine level and MB volume showed significant recovery, suggesting that the damage to the fornix is probably secondary to the MB damage probably representing the Wallerian degeneration. Significantly increased blood thiamine level on follow up in ALF patients suggest that increased blood thiamine level is due to combination of improved liver functions as well as increased dietary intake of thiamine. The poor correlation of blood thiamine level with fornix volume and strong correlation with MB volume further supports the argument that the changes in fornix are probably secondary to the MB insult due to thiamine deficiency, rather than primarily due to thiamine related insult. We conclude that the changes in MBs are primarily related to thiamine deficiency, which may which may secondarily result in microstructural changes in the fornix. These observable changes are known to be specific and may be reversible with restoration of blood thiamine level. These imaging changes may be used as imaging biomarker of thiamine deficiency in these patients in future.

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