Reflections on the Time of Initiating ART in HIV-TB Patients

Sir,

The recently published CAMELIA trial\(^1\) concluded that antiretroviral therapy (ART) should be initiated within 2 weeks of starting anti-TB therapy (ATT). We urge caution, however, in applying the results to patients that do not resemble those in the trial.

The median CD4 counts were 25 in the CAMELIA study. It is surmised that HIV progression may continue because of TB, at an accelerated rate, within the 1st 2-8 weeks thus placing the patient at a higher risk of OI. Will the same considerations apply to patients whose CD4 counts are between 100 and 200?

In the CAMELIA study, IRIS was manageable and was not associated with mortality. But around 68% of cases in CAMELIA were pulmonary TB only. IRIS in pulmonary TB may not demand much clinical support except for patients who develop acute lung injury. However, the situation can be far more difficult in cases of extrapulmonary TB especially tuberculomas in the brain stem, TB meningitis or bulky subarachnoidal lymphadenopathy where patients can have life threatening clinical worsening and require ICU care.

While on one hand, it is difficult to differentiate disease progression due to antimicrobial resistance and IRIS, severe IRIS needs steroids and perhaps other immunosuppression. This can be a major catastrophe if the patient is receiving ineffective ATT due to drug resistance. Only about 2% patients in the CAMELIA trial had MDR TB. In tertiary centre practice in Mumbai and Ahmedabad, however, drug resistant TB appears to be a significant problem although exact prevalence figures are not available. We believe that every effort should be made in all cases to obtain appropriate specimens and demonstrate the susceptibility or resistance of Mtb. These results can only be available after 5 to 8 weeks unless a Line Probe Assay is done and only then can one be sure that the patient is on effective ATT.

The survival difference in the CAMELIA trial only emerged gradually on follow up and the causes of death are not provided. Were they definitely related to HIV? How can additional 2 to 3 weeks of ART have a mortality benefit which appeared after 1 or 2 years? Even if ART had reduced early mortality would it not be by reduction in OI. Can this not be achieved in the short term by screening and prophylaxis for PCP, Toxoplasmosis and Cryptococcosis, as is standard practice?

Starting ART soon after ATT also involves the issue of overlapping dermatological and hepatic toxicity.

The recommendation to start ART 2 weeks after starting ATT to reduce late mortality, based on the CAMELIA study is inappropriate for:

1. Patients with TB meningitis, CNS tuberculomas and bulky mediastinal lymph node disease.
2. Patients started on 1st line ATT but where a suspicion of resistant TB remains, and TB susceptibility result is awaited.
3. Patients with CD4 counts well above 25, somewhere between 100 and 200.
4. If adequate management of IRIS, resistant TB and adverse drug reactions is not always possible.

Adoption of trial results without careful analysis of all mortality data and validation in other settings may become an unwise departure from established practice. The CAMELIA study does not capture the anxiety and anguish of treating a life threatening ‘iatrogenic’ disease like IRIS. The difference between deferred treatment and immediate treatment may mean, in certain situations, the difference between preventing and actually creating a serious condition.

ART initiation after attaining certain clinical milestones such as tolerability of all medication and some clinical response is more useful for the majority of patients seen at our centres rather than at an early fixed time point. Although several strategy trials examining the optimum timing of ART during opportunistic infections have found that early ART is beneficial, the question of the optimum timing clearly has more than one right answer.

Reference


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Received: 02.12.2011; Accepted: 20.01.2012

Hepatic Encephalopathy Masking Myxedema Coma

SIR,

A 72 year old man, known case of alcoholic liver disease since two years was admitted in our hospital with history of unconsciousness since 8 hrs prior to admission. He had ascites for five months and about one liter of ascitic fluid was tapped four days prior to admission. There was no history of fever, jaundice, hematemesis / melena or oliguria. Patient was on treatment with tab Spironolactone 50 mg daily since last five months.

On examination patient was in a state of coma with a Glasgow Coma Score of 3. His vital parameters were normal. Except mild pallor, the physical examination was unremarkable. Abdominal examination revealed ascites, no organomegaly. Neurologically, he was unresponsive, Achilles tendon reflexes were absent bilaterally. Blood investigations on admission showed hemoglobin of 7.3gm%, total leucocyte count of 9,800cells/cmm and adequate platelets. Results of liver chemistry showed: aspartate aminotransferase (AST) 137U/L (upto 40U/L), alanine aminotransferase (ALT) 17 U/L (upto 40U/L), alkaline phosphatase 86 U/L (upto 117U/L), total bilirubin 0.8 mg% (upto 1mg%), direct bilirubin 0.4mg% (upto 0.5mg%), and albumin 2.5 gm% (3-5gm%). The serum ammonia concentration was 94 μmol/L (10–47μmol/L), blood urea nitrogen, serum creatinine and blood sugars were normal. Serum sodium 130mEq/L(123-144), serum potassium 2.9mEq/L (3.6-4.8). Computed tomography of the head revealed mild cerebral atrophy. Ultrasound examination of the abdomen disclosed liver parenchymal disease with coarse echotexture of liver and moderate ascites. Ascitic fluid examination was normal. A diagnosis of cirrhosis of liver with hepatic coma with hyponatremia was made. Treatment of hepatic coma with lactulose, bowel wash and antibiotics was initiated. Hyponatremia was corrected with normal saline. Within 48
hours of treatment, the ammonia level decreased to 40 μmol/L and sodium levels were normal (134mEq/L); but there was no improvement in his mental status. CSF was normal. Because of the poor clinical response; other aetiologies for metabolic encephalopathy were sought. Basal Cortisol level was normal, 9.91 μg/dl (4.30-22.40 μg/dl). His Thyroid function test results done 4 days after admission, revealed severe hypothyroidism (serum thyroid stimulating hormone was >150 μIU/ml (0.4-4 μIU/ml), total T3 was 47.31 ng/dl (81-178 ng/dl) and total T4 was 3.1μg/dl (4.5-12.50μg/dl). Antithyroid peroxidase and antithyroglobulin antibody were negative. Hence, the diagnosis of Myxedema coma was made and patient was started on high dose thyroxine, 300μg per day through yyles tube and injectable steroids (inj hydrocortisone 100 mg intravenously 8 hrly). Over the next 48 hrs, the patient gradually regained consciousness and he started responding to commands.

Discussion

Hyperammonemia, a hallmark of hepatic encephalopathy, has also been described in hypothyroidism. Differentiation between the two conditions, recognition of their possible coexistence, and the consequent therapeutic implications are of utmost importance.

Although the liver is considered to be a hormone independent organ, it is hormone responsive and endocrine alterations affect hepatic function. Hypothyroidism with persistent constipation may exacerbate hyperammonaemia and portosystemic encephalopathy in patients with otherwise well compensated liver disease. Associated hypothyroidism should be considered in a patient with hepatic encephalopathy in presence of unexplained delayed response.

The liver plays an important role in thyroid hormone metabolism being involved in their conjugation, excretion, peripheral deiodination and in synthesis of thyroxine binding globulin. Thyroid test abnormalities are common in both acute and chronic liver disease, but most patients remain euthyroid. The most common abnormalities are increase of total thyroxine and thyroxine binding globulin in association with normal free thyroxine and thyroid stimulating hormone concentrations.1 Hyperammonemia in hypothyroidism may be explained by pathophysiological studies of the urea cycle in this condition. In a rat liver model, hypothyroidism was associated with an increased urea synthesis, attributed to an increase in urea cycle enzyme activity.2 Thyroid dysfunction may also occur in association with chronic liver disease most commonly in immune mediated liver disorders, particularly autoimmune chronic active hepatitis, primary biliary cirrhosis, and hepatitis C.3,4

Differentiation of hypothyroidism from hepatic dysfunction can be difficult, particularly in patients with coexisting liver disease as symptoms of hypothyroidism and chronic liver disease are similar. In both, patients may present with fatigue or mental status changes, as well as weakness, myalgias, and dyspnoea on exertion. Oedema, ascites, and pleural effusion are seen in both disorders. Transaminase increases are common, often with AST raised out of proportion to ALT. While these increases may be caused by the steatosis which has been reported in hypothyroidism, AST increases may also be caused by myopathy.

To date, very few cases of hyperammonemia and myxedema coma have been described in the literature. All cases presented with a clinical picture of hyperammonemic coma, unresponsive to lactulose and neomycin therapy, which improved only after thyroid hormone replacement. Precipitants for hepatic encephalopathy were not evident.5,6

In summary, differentiating hypothyroidism from hepatic dysfunction may occasionally be difficult, particularly in the setting of preexisting liver disease. If suspected portosystemic encephalopathy does not respond to therapy, clinicians should evaluate for coexistent hypothyroidism.

References


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Received: 13.09.2011; Revised: 02.11.2011; Accepted: 08.11.2011