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Original Research Article

Wilsons disease and autoimmune liver disease overlap syndrome: a clinical study

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ABSTRACT

Background: The coexistence of Wilson's disease and autoimmune liver disease in a same patient is a rare entity. Combined treatment with steroid and D-penicillamine may be effective. Aim of the study was analyse the clinical, histological, laboratory profile for patients with chronic liver disease with aim of finding the etiology of the disease.
Methods: It is an observational study. Common clinical presentations were evaluated. Laboratory investigations done include complete blood count, renal and liver function tests, prothrombin time, viral markers for hepatitis A, B, C and E, USG abdomen and pelvis, portal Doppler studies and upper GI endoscopy. Specific tests include ANA, AMA, ASMA, Anti LKM-1Ab, serum ceruloplasmin and 24hrs urinary copper were done. Liver biopsy was done in selected patients.
Results: Commonest clinical presentation was abdominal distension (80%), abdominal pain (30%), pedal edema (60%), splenomegaly (40%) and upper GI bleed (40%). Laboratory investigation revealed anemia (50%), thrombocytopenia (70%), prothrombin time prolongation in (60%), normal liver function in 60%, abnormal liver function in (40%). Autoimmune markers revealed ANA strong positivity in (40%), mild positivity in (60%). AMA, ASMA, Anti-LKM-1 were negative in all cases (100%). Liver biopsy showed features of autoimmune liver disease and Periportal copper deposition in 80% of cases.
Conclusions: Coexistence of Wilson's disease and autoimmune liver disease is a rare entity and medical treatment with steroids and D-penicillamine simultaneously to be started in these patients.

Keywords: Autoimmune liver disease, Overlap, Wilson's disease

INTRODUCTION

Clinical, serological, histological and radiological features overlap in Autoimmune Hepatitis, but appropriate diagnosis remains hindered by a lack of standardized diagnostic criteria. So patients should be carefully counseled with regard to the risks and benefits of treatment, bearing in mind the paucity of randomized and controlled outcome data for medical interventions.[1]

The coexistence of Wilson's disease (WD) and Autoimmune Liver Disease (ALD) in same patients is a rare entity.[2,3] Hepatocyte necrosis and intracellular antigen exposure to immune system is seen in WD and results in low titer autoantibody production.[4] Therefore, it is highly recommended to screen WD in patients labelled as AIH, especially when the response to treatment with immunosuppressant drugs is disappointing. In this

situation, combined treatment with steroid and d-penicillamine may be effective.

Aim of the research work was to study the clinical, histological, laboratory profile in patients with chronic liver disease over a period of 1 year with aim of finding the etiology of the disease after ruling out common causes like alcohol, viruses and drugs.

METHODS

It is an observational study done in a rural centre in South India. All patients who were admitted to the Department of Medical Gastroenterology, Government Thoothukudi Medical College Hospital with a diagnosis of chronic liver disease both by clinical features and by investigations were evaluated for the etiology of the same.

Inclusion criteria

All patients who had evidence of chronic liver disease and who had positive tests for both Wilson's disease and autoimmune hepatitis were included in the study.

Exclusion criteria

The following patients who fulfilled features for both autoimmune hepatitis and Wilsons's Disease were excluded if:

- They were positive for viral markers,
- They have evidence for any other etiology of chronic liver disease like non-cirrhotic portal fibrosis of extra hepatic portal venous obstruction, etc.

Procedure

Total of 10 patients fulfilled the criteria for inclusion in this study. All these 10 patients were subjected for complete clinical and laboratory evaluation.

Laboratory investigations done in all patients include complete blood count, renal and liver function tests, prothrombin time, viral markers for hepatitis A, B, C and E, USG abdomen and pelvis, portal Doppler studies and upper GI endoscopy.

Specific tests include ANA, AMA, ASMA, Anti LKM-1 Ab, serum ceruloplasmin and 24hrs urinary copper were done in selected situations. ANA, AMA, ASMA and Anti LKM-1 Ab were done by using newer generation ELISA method. 24-hour urine copper and serum copper estimations were done with spectrophotometry. Serum ceruloplasmin was done with immunoturbidimetry assay. Liver biopsy for assessing the severity and prognosticating was done in selected patients and special staining for copper and iron were done if required.

RESULTS

All the patients in whom we could complete the workup including liver biopsy were included in the study. Total of 10 patients fulfilled the criteria for inclusion in this study. Out of 10 patients 6 were males and 4 were females. Commonest clinical presentations were abdominal distension (80%), abdominal pain (30%), pedal edema (60%), splenomegaly (40%) upper G.I. bleed (40%) (Figure 1).

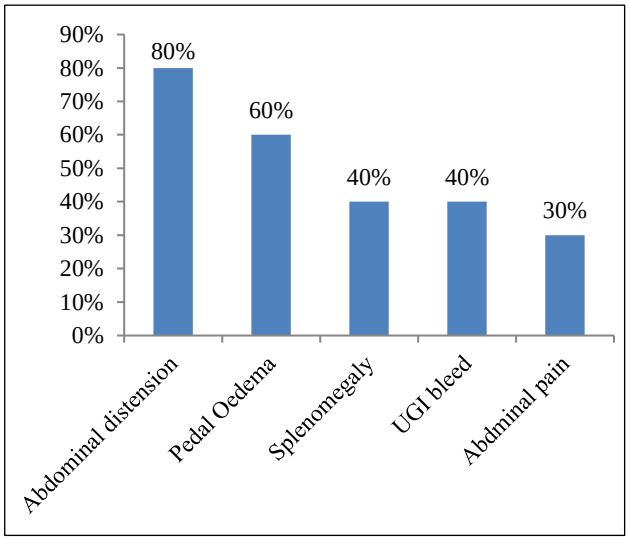

Figure 1: Distribution of clinical presentation.

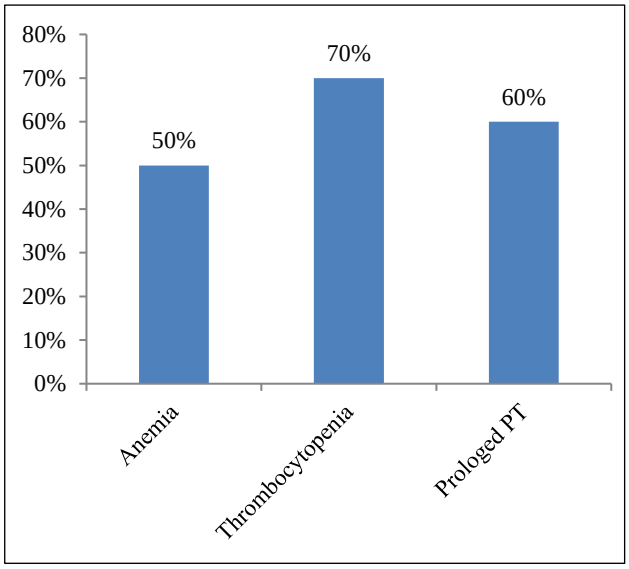

Figure 2: Laboratory investigations.

Laboratory investigation revealed anemia (50%), thrombocytopenia (70%), prothrombin time prolongation (60%) (Figure 2). Normal liver function (60%), abnormal liver function (40%). Hepatitis A, B, C and E were negative in all the cases (100%). Serum ceruloplasmin was <20mg% in 30%, normal ceruloplasmin level in 70%. 24hours urinary copper level range of >200 in

(40%), 100-200 in 40%, 90-100 in 20%. Autoimmune markers revealed ANA strong positivity in 40%, mild positivity in 60%. AMA, ASMA, Anti-LKM-1 were negative in all cases (100%). Liver biopsy showed features of autoimmune liver disease and periportal copper deposition in 80% of cases (Figure 3 to 6). The portal tracts and septa show expansion with mild to moderate inflammatory cells comprising of lymphocytes, few eosinophils and polymorphs. Stainable granules of copper/copper associated proteins are noted in hepatocytes.

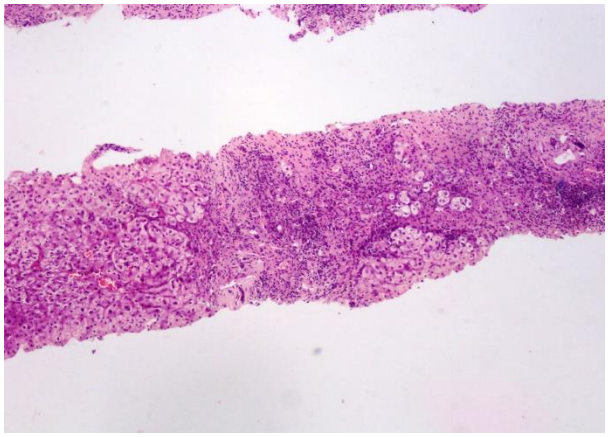

Figure 3: Liver biopsy low power.

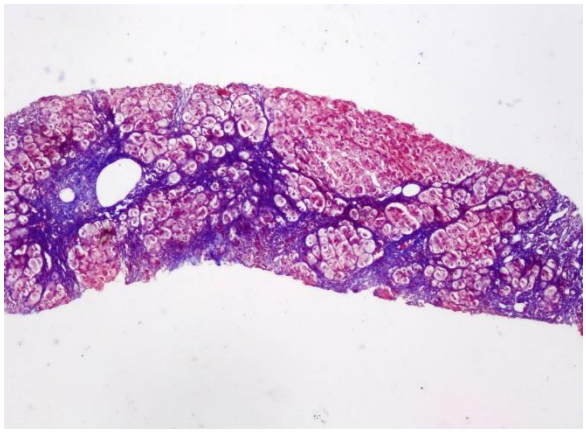

Figure 4: Liver biopsy low power.

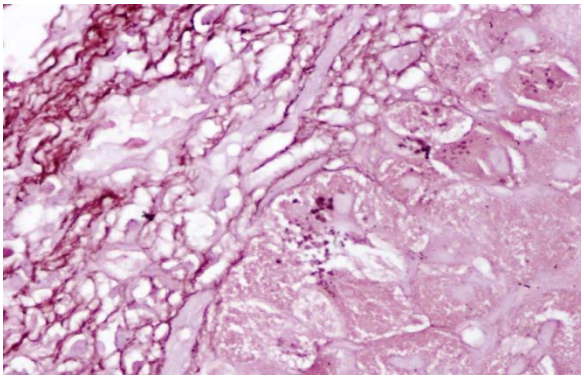

Figure 5: Liver biopsy high power.

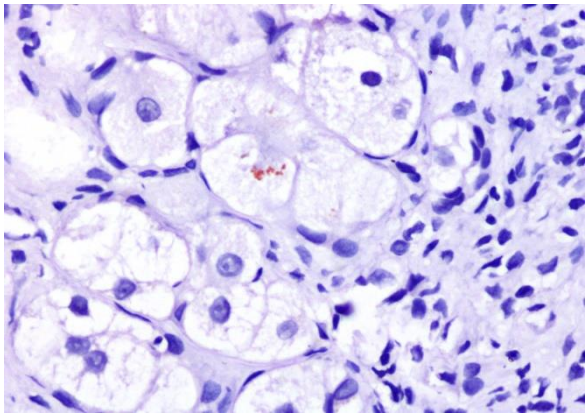

Figure 6: Liver biopsy high power.

DISCUSSION

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are considered as a single entity called autoimmune liver diseases. Immune mediated liver injury leads to varied clinical presentations in this setting. Some patients have evidence of either PBC or PSC with overlapping features of AIH.[1] Conditions having features of two different autoimmune liver diseases are grouped as 'Overlap Syndromes'.[3] But there is no current agreement on what are the specific diagnostic criteria for an overlap.[4] Type-I AIH has anti-nuclear antibodies (ANA) and/or anti-smooth muscle antibodies (ASMA), whilst type-II AIH is has anti-liver kidney microsomal type-1 (anti-LKM-1) antibodies. Anti-soluble liver-pancreas antigen (SLA/LP) antibodies (directed against a selenocysteinyl-transfer RNA synthase) represents a third subgroup of AIH patients, being clinically indistinguishable from those with type-I disease.[5] In a genetically predisposed individual, an environmental trigger may lead to development of neo-autoantigen, which are recognised by nonpolarised T cells (via an antigen-presenting cell) resulting in cellular activation.[4] Once activated, and depending upon the cytokine milieu, activated intrahepatic T-helper cells promote the differentiation of cytotoxic T cells, Th17 cells, and/or the differentiation of B cells into plasma cells which produce immunoglobulins and together with the activation of monocytes contributes to the loss of self-tolerance and increasing chronic inflammatory tissue damage.[6]

But overlapping features of Wilson's disease with Autoimmune Liver disease is rarely reported. Hepatocyte necrosis and intracellular antigen exposure to immune system is seen in WD which results in low titre of autoantibody production.[7] Autoantibody can be positive in WD due to hepatocyte necrosis, especially in early stage of this disease.[8] There are several cases of WD that were initially diagnosed as AIH and have only partial response to treatment with steroids and azathioprine. Due to an absence of well-validated diagnostic criteria and absence of large therapeutic trials, treatment of overlap conditions is empiric and extrapolated from data derived

from the primary autoimmune liver diseases.[9] Therefore, it is better to consider medical therapy for both the conditions, in a setting with dominant features of both Wilson's disease and autoimmune hepatitis, at the same time.[10]

CONCLUSION

The coexistence of Wilson's disease and autoimmune liver disease is a rare entity and clinician should have high level of suspicion in diagnosing the problem. Treatment with steroids and D-penicillamine simultaneously may be beneficial in these patients for better response.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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