Original Article

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Autoimmune Hepatitis in Children: Experiences in a Tertiary Center

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Abstract

Objective: Autoimmune hepatitis (AIH) is a necroinflammatory liver disease of unknown etiology that occurs in the children of all ages. The present study aimed to evaluate the clinical and paraclinical presentations, including pattern of autoantibodies, response to treatment, mortality, and liver transplantation outcome in the Iranian children with AIH.

Methods: The medical records of 87 children (56 girls and 31 boy) diagnosed with AIH between 2001 and 2010 were retrospectively analyzed for clinical and paraclinical profiles and also treatment outcome.

Findings: The mean age of the patients was 10.1±4.5 years (64.4% females). The most common clinical findings were jaundice (70.1%), splenomegaly (67.8%), and hepatomegaly (51.7%). Antinuclear, anti-smooth muscle, and anti LKM antibodies were positive in 14/62, 22/53 and 6/40 patients, respectively (36 patients had type 1 AIH, 6 patients had type 2 AIH, 26 patients were seronegative, and autoantibodies were not available in 19 cases). The most common histological finding in the liver biopsies was chronic hepatitis with interface activity that was seen in 65 (74.7%) patients. The complete response was seen in 52 (59.8%) patients and 24 (27.6%) patients underwent liver transplantation. One-year and five-year survival rates were 87.5% and 80% in the transplanted patients.

Conclusion: AIH should be kept in mind in the differential diagnosis of both acute and chronic liver diseases in the children and treatment with combination of corticosteroids and azathioprine is a good treatment option. In the patients with end stage liver cirrhosis that did not respond to medical therapy, liver transplantation is the treatment of choice.

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Key Words: Autoimmune Hepatitis; Autoantibody; Liver Function Tests; Liver Transplantation

Introduction

Autoimmune hepatitis (AIH) is a form of chronic hepatitis which affects the patients who have lost their immunological tolerance to liver-specific antigens[1-6]. AIH has a broad clinical spectrum including asymptomatic individuals with abnormal laboratory results, clinical symptoms similar to those of acute viral hepatitis, and hepatic insufficiency or even cirrhosis[2]. The diagnosis of the disease is based on the clinical and laboratory findings as well as the exclusion of other causes of chronic liver diseases. AIH is more frequent in females and is associated with hypergammaglobulinemia, elevated serum transaminase activity, positive organ and non-

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organ specific autoantibodies, and histological picture of interface hepatitis and also may be associated with other autoimmune disorders in the patients as well as their first-degree relatives[6]. There are two types of AIH according to their serology: type 1 is characterized by presence of anti-nuclear (ANA) and/or anti-smooth muscle (ASMA) antibodies, while type 2 is characterized by presence of anti-liver kidney microsomal type 1 (anti LKM) antibody. Immunosuppressive therapy with corticosteroids, usually in combination with azathioprine is considered the gold standard to induce and maintain remission[7,8]. Overall, the treatment goal is to maintain aminotransferases at the normal level or not twice higher than the reference value and, at the same time, reduce the inflammatory infiltrate within the liver[7,9-12]. Nevertheless, some patients do not respond to immunosupressive treatment and might require liver transplantation[13]. AIH is a well-documented issue in the West; however, limited literature is available on this subject in the Middle East. Therefore, in this report we present clinical, laboratory features and treatment outcome of 87 Iranian children with AIH.

Subjects and Methods

The medical records of all the children less than 18 years old who were diagnosed and treated as AIH in the Pediatric Hepatology Ward affiliated with Shiraz University of Medical Sciences between 2001 and 2010 were reviewed. The diagnosis was established according to the International Autoimmune Hepatitis Group scoring system published in 1993[2] and Simplified Criteria for the Diagnosis of Autoimmune Hepatitis in 2008[14]. All the patients with hepatitis due to other causes such as viral hepatitis and metabolic disorders were excluded from this study.

Overall, 87 children and adolescents with definite (n=68; 78.2%) or probable (n=19; 21.8%) diagnosis of AIH were entered into the present study. The paraclinical tests, including serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), serum bilirubin, and plasma proteins and auto antibody tests, including immunofluorescence for ANA and ASMA and enzyme immunoassay for anti LKM antibody were extracted from the medical files. The reference values for ALT and AST were considered from 15 to 35 U/L and for serum globulin levels from 1.0 to 1.5 g/dL. In addition, anti LKM and ASMA titer exceeding 1:20 and ANA ≥1:40 were considered as positive according to the manufacturer guideline.

Percutaneous needle liver biopsy was taken if the clinical and laboratory profiles permitted. Seventy-nine patients underwent liver biopsy before treatment and in 8 patients liver biopsy was possible between 1 and 6 months after starting treatment. The treatment regimen consisted of a combination of prednisone and azathioprine given at 1 to 2 mg/kg/day (maximum 60 mg/day) and 1.5 mg/kg/day (maximum 100 mg/day), respectively. The reassessment was performed weekly up to 4-6 weeks when the dose of prednisone was reduced by a 5-mg reduction per week up to the minimum dose keeping the patients in clinical and laboratory remission (5-7.5 mg/day). If patients did not respond to this treatment we considered calcineurin inhibitors or mycophenolate mofetil. Treatment response was assessed according to the criteria established by the International Autoimmune Hepatitis Group published in 1993[2]. For those not responding to the all above mentioned treatment and progressed to decompensated cirrhosis, liver transplantation was considered.

All the results were expressed as mean (±standard deviation). The data were statistically analyzed using Student's t-test. In addition, *P* values less than 0.05 were considered as statistically significant. The statistical analysis was done using the SPSS statistical software (version15.0).

Findings

Among the 87 patients, 56 (64.4%) were females. The mean age of the patients was 10.1±4.5 years (range, 4 months to 18 years) at the time of diagnosis. The most common clinical presentations were jaundice (n=76; 87.4%), tea color urine (n=51; 58.6%), vomiting (n=41;

Table 1: The clinical presentations of patients with autoimmune hepatitis

Clinical history	Number (%)
Jaundice	76 (87.4)
Dark urine	51 (58.6)
Vomiting	41 (47.1)
Abdominal pain	39 (44.8)
Nausea	38 (43.7)
Malaise	33 (37.9)
Anorexia	33 (37.9)
Hematemesis	23 (26.4)
Pale stool	16 (18.4)
Melena	12 (16.1)
Weight loss	7 (13.8)
Chronic diarrhea	6 (6.9)
Fatigue	3 (3.4)
Headache	1 (1.1)
Hematuria	1 (1.1)

47.1%), and abdominal pain (n=39; 44.8%). Other clinical presentations are shown in Table 1.

Physical examination revealed jaundice in 61 (70.1%) patients, splenomegaly in 59 (67.8%), hepatomegaly in 45 (51.7%), abdominal collateral veins in 18 (20.7%), and palmar erythema in 17 (19.5%) patients (Table 2). Overall 61 (70.1%) patients presented with chronic liver diseases, 14 (16.1%) with acute hepatitis, 9 (10.3%) cases with asymptomatic liver enzyme elevation and three (3.4%) patients presented with fulminant hepatitis. Four (4.6%) patients had overlap syndrome with primary sclerosing cholangitis, three of them had also ulcerative colitis. One patient had concomitant hypothyroidism.

The family history of the other associated autoimmune diseases was positive in 9 (10.3%)

Table 2: The frequency of clinical findings in patients with autoimmune hepatitis

Physical examination	Number (%)
Jaundice	61 (70.1)
Splenomegaly	59 (67.8)
Hepatomegaly	45 (51.7)
Collateral veins	18 (20.7)
Palmar erythema	17 (19.5)
Spider nevi	10 (11.5)
Clubbing	9 (10.3)
Striae	5 (5.7)
Leukonychia	2 (2.3)

patients, AIH in 4 (4.6%), diabetes mellitus in 3 (3.4%), systemic lupus erythematous and primary hyperparathyroidism each in one (1.2%) patient.

The laboratory findings are listed in Table 3. The most common paraclinical findings were elevated ALT (mean; 347±607 U/L) and AST (mean; 405±622 U/L) that was seen in all patients. The mean serum globulin level was 3.98±1.1 g/dL. The autoantibodies including ANA, ASMA, and anti LKM were positive in 14/62 (22.6%), 22/53 (41.5%), and 6/40 (15%) patients, respectively. Besides, the presence of ASMA and ANA together was detected in six patients. According to the available autoantibodies (68/87 patients) 36 patients were classified as having type I AIH (mean age: 10.6±4 years; 69.4% females) and 6 patients as type II AIH (mean age: 8.6±5.1 years; 50% females). Twenty-six (29.9%) patients were seronegative. The autoantibodies were not available in 19 patients. The main results of the histopathological evaluation of the liver biopsies were chronic hepatitis with lymphocyte and plasma cell infiltration and interface hepatitis that was seen in 65 (74.7%) patients which was compatible with the diagnosis of AIH. In these patients inflammation was graded between 1 and 6 in 13 (20%), 7-12 in 41 (63.1%), and 13-18 in 11 (16.9%) patients, also fibrosis was staged between 1 and 2 in 22 (33.8%), 3-4 in 21 (32.3%), and 5-6 in 22 (33.8%) patients (modified HAI of Ishak). Initial liver biopsy was reported as cirrhosis in 22 (25.3%) patients. Repeat liver biopsy was done in 51 patients that remained in clinical and biochemical remission after 2-3 year immunosuppressive treatment and showed non-specific pathologic changes in 38 patients, decreased inflammation and fibrosis in 6, worsening of inflammation in 4, and cirrhosis in 3 patients. Treatment was stopped in 38 patients with normal liver pathology and they were without any relapse after 33.1±16.6 (7-67) months follow up. Overall, one month after starting immune suppressive therapy, 52 patients achieved normal liver enzyme levels and became symptoms free, so complete response was observed in 59.8% of patients. Of those who did not respond to standard therapy 5 patients responded to mycophenolate mofetil and 3 to cyclosporine and 2 patients to tacrolimus. None of the three patients that presented with fulminant

Table 3: The laboratory findings of children with autoimmune hepatitis

Parameter	Minimum	Maximum	Mean (SD)
Total protein (g/dL)	5.5	10.4	7.35 (1.1)
Albumin (g/dL)	2	5.3	3.61 (0.9)
Globulin (g/dL)	2	7.6	3.98 (1.1)
Aspartate aminotransferase (U/L)	120	3125	405 (622)
Alanine aminotransferase (U/L)	112	3760	347 (607)
Alkaline phosphatase (U/L)	84	2585	765 (516)
Total bilirubin (mg/dL)	0.3	60.7	10.39 (13)
Direct bilirubin (mg/dL)	0.1	37.3	4.37 (6.4)
Prothrombin time (seconds)	12	60.9	18.31 (7.6)
International Normalized Ratio	0.84	12	2.15 (1.9)
White blood cell (/mm^3)	1200	14800	6412 (3030)
Hemoglobin (g/dL)	6.4	18.8	11.3 (2.1)
Platelets (/mm^3)	9100	1103000	194000 (163000)
Erythrocyte sedimentation rate	1	110	27.17 (25.1)

SD: standard Deviation

hepatic failure responded to medical treatment and two patients underwent liver transplantation and another one expired while awaiting a liver transplant. Also, none of the patients with liver cirrhosis in the initial liver biopsy responded to the treatment, and so, were candidate for liver transplantation. Overall 4 (4.6%) patients expired, 3 due to post transplantation complications and one as a result of the severity of the disease and hepatic encephalopathy. Two cases with liver transplantation developed chronic rejection due to non-compliance and one of them also had ulcerative colitis. One-year and five-year survival rates were 87.5% and 80%, respectively in the transplanted patients.

Discussion

Autoimmune hepatitis is a chronic necro-inflammatory disease of unknown etiology; a few studies have been conducted on the children in this regard[15-19]. AIH has a one peak age of presentation around 10 years, the mean age of our patients was 10.1 years that was comparable with other studies[16,17]. The disease is more common in females; about two thirds of the patients in this series were females, similar to other studies[16,17,20]. Children with AIH may present with non-specific symptoms of varying severity, such as anorexia, nausea, abdominal pain, malaise, fatigue, lethargy, and itching. Arthralgia of the small joints is also a common symptom. In the present study more than one third of the cases presented with anorexia, nausea, abdominal pain, and malaise. None of our cases had arthralgia. These results are in line with other researches[15,20]. Physical examination may be without significant findings, but jaundice, hepatomegaly, splenomegaly, and stigmata of chronic liver disease may also be found[1,21]. More than half of the patients in our study had jaundice, hepatomegaly, and splenomegaly. In addition, diseases with an autoimmune background such as ulcerative colitis, type 1 diabetes mellitus, thyroiditis, and celiac disease are more frequently seen in the patients with AIH[22]. The associated autoimmune disorders were not common in this study as 3 patients had ulcerative colitis and only one case had hypothyroidism. In general, the disease can have different presentations, including asymptomatic with isolated elevation of aminotransferase, having an insidious, sometimes fluctuating clinical course, and similar to acute hepatitis or fulminant liver failure. An undistinguishable clinical status of acute viral hepatitis can be the initial manifestation in 40 to 70% of the patients with AIH[4,14,23-25]. The role of autoantibodies in the pathogenesis of AIH is not known completely. AIH is a liver specific disease and non-liver specific autoantibodies are unlikely to be involved in the inflammation and damage to the liver. ANA, ASMA and anti LKM autoantibodies are highly sensitive but not specific for AIH. ANA

and ASMA have also been observed in chronic viral hepatitis B and C in low titers. Also, ASMA is present in non-autoimmune inflammatory hepatic diseases and in autoimmune diseases not affecting the liver. Anti LKM autoantibody can be found in hepatitis C patients. So, the diagnosis of AIH should not be based exclusively on autoantibody testing but on the presence of a combination of characteristic clinical, laboratory, and histological findings[26]. However, the identification of clinical relevant autoantibodies provides a valuable diagnostic aid but their absence is not enough to rule out the disease[17] as 29.9% of our cases were seronegative. The negativity for ANA, ASMA and anti LKM is reported in the literature in 20 to 30% of the cases of AIH [17]. The rate of ASMA positivity in this study is comparable with Ferreira AR et al[17] (41.5% vs 52.8%) but ANA was positive in 22.6% of our cases whereas 66.7% of patients in Ferreira AR et al[17] series were ANA positive. Regarding anti LKM antibody the rate of positivity was higher in the present study (15% vs 3%). The rate of seropositivity was higher in a similar study conducted on children with AIH in Iran by Rafeey M et al in 2007[16]. Since there is no single test confirming the diagnosis of AIH, liver biopsy remains of most importance. In 1992, the International Autoimmune Hepatitis Group recommended a scoring system for the diagnosis of AIH to allow reliable diagnosis of the disease, and this was further updated in 1999[27]. The sensitivity of the scoring system for diagnosis of AIH is reported from 97% to 100%. We used simplified criteria for the diagnosis of AIH established by Hennes et al in 2008[14]. All of our patients had simplified score ≥6. The laboratory findings which suggest AIH are hypergammaglobulinemia, elevated titers of autoantibodies, and the increased amount of aminotransferases. All of patients in this study had elevated liver enzymes and serum globulin levels more than 2 gr/dL that is comparable with Saadah et al study[20]. AIH should be differentiated from other causes of chronic liver diseases and viral hepatitis[2,24,28-31]. Histopathological lesions found in the AIH may vary depending on the level and stage of the disease. The histological findings of AIH are the same as that of other chronic hepatitis, and although certain findings are characteristic, no findings are specific for AIH. AIH is generally characterized by a mononuclear-cell infiltrate that invade the limiting plate (periportal infiltrate; or interface hepatitis). These findings were seen on 74.7% of our cases. Also, there may be an abundance infiltration of plasma cells and/or eosinophils. In advanced disease, fibrosis is extensive, with the distortion of the hepatic lobule and the appearance of regenerative nodules, and indeed the presence of complete or incomplete cirrhosis is the most common finding at diagnosis, with a frequency of 59% to 100% among the pediatric patients[19-33]. In our study, this frequency was 25.3%. If left untreated, severe AIH has a very high mortality rate of up to 50% after 3-5 years of diagnosis[34]. Immunosuppressive therapy with corticosteroids, usually in combination with azathioprine is considered the gold standard to induce and maintain remission. In addition, response to immunosuppressive medications confirms the diagnosis of AIH[35]. Therapeutic response is assessed through the improvement of signs, symptoms, and the liver function tests. The therapeutic goal should be complete normalization of transaminases because progression to liver cirrhosis may occur in the patients with residual inflammatory activity within the liver[36].

Under immunosuppression, most of the patients achieve complete remission as we saw 59.8% response rate in our series. This complete response rate is lower than that reported by others[17]. There are only a few evidences for how long maintenance therapy should be given; it seems that children with AIH should be in stable remission for at least 3-4 years before withdrawal of immunosuppressive therapy can be considered[37]. We stopped immunosuppressive therapy in 38 patients without any relapse. Although some patients do present with fulminant hepatic failure and may need liver transplantation[38], the ultimate prognosis of AIH is mostly determined by response to immunosuppressive therapy. It should be noted that treatment failures occur in about 20% of patients with AIH and that it is more frequent in those with established cirrhosis and in general, the prognosis is inversely correlated with the histological severity of the disease as none of the cases with established cirrhosis in the initial liver biopsy in the present study responded to immunosuppressive therapy. The best treatment option for these patients is liver transplantation

with promising outcome. One-year and five-year survival rates in the patients who underwent liver transplantation due to AIH was 87.5% and 80%, respectively in our tertiary center. Indeed, the lower mortality rate (4.6%) in our series compared to others[15,17] is due to liver transplantation facilities.

Conclusion

AIH in children has a wide spectrum of clinical presentation that extends from the absence of symptoms to an acute and even fulminant hepatic failure. Although considered uncommon, AIH should be kept in mind in the differential diagnosis of both acute and chronic liver diseases of children after excluding the other causes of liver diseases. If left untreated, AIH progresses to cirrhosis with high mortality, but early diagnosis and treatment prolong survival.

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Conflict of Interest: None

References

1. Krawitt EL. Autoimmune hepatitis. *N Engl J Med* 2006;354(1):54-66.
2. Johnson P, McFarlane IG. Meeting report: International autoimmune hepatitis group. *Hepatology* 1993;18(4):998-1005.
3. Vergani D, Mieli-Vergani G. Aetiopathogenesis of autoimmune hepatitis. *World J Gastroenterol* 2008; 14(21):3306-12.
4. Donaldson PT. Genetics of autoimmune and viral liver diseases; understanding the issues. *J Hepatol* 2004;41(2):327-32.
5. Longhi MS, Mitry RR, Samyn M, et al. Vigorous activation of monocytes in juvenile autoimmune liver disease escapes the control of regulatory T-cells. *Hepatology* 2009;50(1):130-42.
6. Longhi MS, Hussain MJ, Mitry RR, et al. Functional study of CD4+ CD25+ regulatory T cells in health and autoimmune hepatitis. *J Immunol* 2006;176(7): 4484-91.
7. Czaja AJ. Treatment of autoimmune hepatitis. *Semin Liver Dis* 2002;22(4):365-78.
8. Johnson PJ, McFarlane IG. Meeting report: International autoimmune hepatitis group. *Hepatology* 1993;18(4):998-1005.
9. Czaja AJ, Freese DK. Diagnosis and treatment of autoimmune hepatitis. *Hepatology* 2002;36(2):479-97.
10. Burak KW, Urbanski SJ, Swain MG. Successful treatment of refractory type 1 autoimmune hepatitis with methotrexate. *J Hepatol* 1998;29(6):990-3.
11. Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010;51(6):2193-213.
12. Azhar A, Niazi MA, Tufail K, et al. A new approach for treatment of hepatitis C in hepatitis C-autoimmune hepatitis overlap syndrome. *Gastroenterol Hepatol* 2010;6(4):233-6.
13. Sanchez-Urdazpal L, Czaja AJ, van Hoek B, et al. Prognostic features and role of liver transplantation in severe corticosteroid-treated autoimmune chronic active hepatitis. *Hepatology* 1992;15(2): 215-21.
14. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* 2008;48(1):169-76.
15. Sotelo N, López G. Autoimmune-type chronic active hepatitis in children. A report of 23 cases at a hospital in northwestern Mexico. *Ann Hepatol* 2005; 4(4):255-60.
16. Rafeey M, Kianrad M, Hasani A. Autoimmune hepatitis in Iranian children. *Indian J Gastroenterol* 2007;26(1):11-13.
17. Ferreira AR, Roquete MLV, Penna FJ, et al. Autoimmune hepatitis in children and adolescents: clinical study, diagnosis and therapeutic response. *J Pediatr (Rio J)* 2002;78(4):309-14.
18. Mieli-Vergani G, Vergani D. Autoimmune liver diseases in children - What is different from adulthood? *Best Pract Res Clin Gastroenterol* 2011; 25(6):783-95.
19. Roberts EA. Autoimmune hepatitis from the paediatric perspective. *Liver Int* 2011;31(10):1424-31.
20. Saadah OI, Smith AL, Hardikar W. Long-term outcome of autoimmune hepatitis in children. *J Gastroenterol Hepatol* 2001;16 (11):1297-302.

21. Czaja AJ. Variant forms of autoimmune hepatitis. *Curr Gastroenterol Rep* 1999;1(1):63-70.
22. Obermayer-Straub P, Perheentupa J, Braun S, et al. Hepatic autoantigens in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *Gastroenterology* 2001;121(3):668-77.
23. Clifford BD, Donahue D, Smith L, et al. High prevalence of serological markers of autoimmunity in patients with chronic hepatitis C. *Hepatology* 1995;21(3):613-9.
24. Lohse AW, Gerken G, Mohr H, et al. Relation between autoimmune liver diseases and viral hepatitis: clinical and serological characteristics in 859 patients. *Z Gastroenterol* 1995;33(9):527-33.
25. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* 2008;48(1):169-76.
26. Vergani D, Alvarez F, Bianchi FB, et al. International Autoimmune Hepatitis Group. Liver autoimmune serology: a consensus statement from the committee for autoimmune serology of the International Autoimmune Hepatitis Group. *J Hepatol* 2004;41(4):677-83.
27. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999;31(5):929-38.
28. Eggink HF, Houthoff HJ, Huitema S, et al. Cellular and humoral immune reactions in chronic active liver disease. I. Lymphocyte subsets in liver biopsies of patients with untreated idiopathic autoimmune hepatitis, chronic active hepatitis B and primary biliary cirrhosis. *Clin Exp Immunol* 1982;50(1):17-24.
29. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995;22(6):696-9.
30. Ferri PM, Ferreira AR, Miranda DM, et al. Diagnostic criteria for autoimmune hepatitis in children: a challenge for pediatric hepatologists. *World J Gastroenterol* 2012;18(33):4470-3.
31. Neuhauser M, Bjornsson E, Treeprasertsuk S, et al. Autoimmune Hepatitis-PBC Overlap Syndrome: A simplified scoring system may assist in the diagnosis. *Am J Gastroenterol* 2010;105(2):345-53.
32. Czaja AJ, Manns MP. Advances in the diagnosis, pathogenesis, and management of autoimmune hepatitis. *Gastroenterology* 2010;139(1):58-72.
33. Gregorio GV, Portmann B, Karani J, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: A 16-year prospective study. *Hepatology* 2001;33(3):544-53.
34. Soloway RD, Summerskill WH, Baggenstoss AH, et al. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. *Gastroenterology* 1972;63(5):820-33.
35. Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. *N Engl J Med* 1995;333(15): 958-63.
36. Ferreira AR, Roquete MLV, Toppa NH, et al. Effect of treatment of hepatic histopathology in children and adolescents with autoimmune hepatitis. *J Pediatr Gastroenterol Nutr* 2008;46(1):65-70.
37. Kanzler S, Gerken G, Lohr H, et al. Duration of immunosuppressive therapy in autoimmune hepatitis. *J Hepatol* 2001;34(2):354-5.
38. Larsen FS. Treatment of patients with severe autoimmune hepatitis. *Minerva Gastroenterol Dietol* 2008; 54(1):57-63.