1130-0108/2007/99/5/255
Revista Española de Enfermedades Digestivas

Rev Esp Enferm Dig (Madrid)
Vol. 99. N.° 5, pp. 255-258, 2007

ORIGINAL PAPERS

Autoimmune hepatitis in pediatric patients

R. García Romero, J. Martín de Carpi, C. Bernal Cuartas, S. Pinillos Pisón and V. Varea Calderón

Section of Pediatric Gastroenterology, Hepatology and Nutrition. Hospital Sant Joan de Déu. Barcelona, Spain

RESUMEN

Introducción: la hepatitis autoinmune es una enfermedad inflamatoria de origen desconocido responsable de una destrucción progresiva del hígado y evolución hacia la cirrosis.

Objetivo: el objetivo es evaluar las características de las hepatitis autoinmunes en la población infantil.

Material y métodos: estudio retrospectivo de pacientes diagnosticados en nuestro servicio en los últimos 10 años. Las variables analizadas son: edad, sexo, forma de presentación, función hepática, inmunoglobulinas, autoinmunidad, histología, tratamiento, necesidad de trasplante y evolución clínica. Según la positividad de los auto-anticuerpos se clasifican en tipo I (ANA y/o ASMA) y tipo II (LKM-1).

Resultados: se diagnostica a siete pacientes, 5 mujeres (71,5%) y 2 varones (28,5%); tipo I 5 y tipo II dos pacientes. La edad al diagnóstico es 21 meses a 12 años. En el tipo I la presentación clínica es como hepatitis aguda en 3 casos y 2 pacientes con insuficiencia hepática progresiva. Las tipo II se diagnostican tras un hallazgo analítico siendo asintomáticas. La elevación de transaminasas (x10 su valor) se observa en el 71,5% e hipergammaglobulinemia en el 85%. El tratamiento instaurado es azatioprina y corticosteroides con un tiempo medio de remisión de 14 meses. Dos pacientes recaen al retirar corticosteroides.

Conclusión: las formas de presentación son variadas y puede ser indistinguible a una hepatitis viral. Se debe sospechar ante una elevación de las aminotransferasas y la presencia de hipergammaglobulinemia. Con buenos resultados el tratamiento recomendado sería azatioprina y corticosteroides. Existen altos porcentajes de recaídas al retirar la corticoterapia por lo que algunos pacientes precisarían de dosis mínimas para mantener la remisión.

Palabras clave: Hepatitis autoinmune. Hipergammaglobulinemia. Cirrosis. Azatioprina.

ABSTRACT

Background: autoimmune hepatitis (AIH) is an inflammatory disease of unknown origin that is responsible for progressive liver necrosis and ultimately cirrhosis.

Objective: our aim was to evaluate the characteristics of autoimmune hepatitis presenting in the pediatric age.

Material and methods: we conducted a retrospective study of all patients diagnosed with AIH in our hospital department during the last 10 years. Variables analyzed included age, sex, clinical presentation, hepatic function, immunoglobulins, autoimmunity markers, histology, treatment, need for transplant, and clinical evolution. According to the positive level of auto-antibodies, AIH patients were classified as type I AIH (ANA and/or smooth-muscle antibodis) and type II (anti-LKM-1).

Results: seven patients were diagnosed in this period –5 girls (71.5%) and 2 boys (28.5%). Five patients presented with type-I serological markers, and two with type-II markers. Age range at diagnosis was from 21 months to 12 years. In the type-I group, 3 patients presented with acute hepatitis while 2 other patients were diagnosed from laboratory findings while asymptomatic. Elevated aminotransferase (10 times the normal level) was observed in 71.5%, and 85% had elevated immunoglobulins. Treatment with azathioprine and prednisone was started after diagnosis with an average time to remission of 14 months. Two patients relapsed following steroid withdrawal.

Conclusion: AIH can have different forms of clinical presentation, and is sometimes indistinguishable from viral hepatitis. AIH must be ruled out in patients presenting with concomitant elevation of aminotransferases and immunoglobulins. The commonly accepted treatment is a combination of azathioprine and corticosteroids. A high percentage of patients experience a relapse of disease after steroids are withdrawn. Therefore, some patients will need to stay on combined therapy with minimal doses of steroids.

Key words: Autoimmune hepatitis. Hypergammaglobulinemia. Cirrhosis. Azathioprine.

García Romero R, Martín de Carpi J, Bernal Cuartas C, Pinillos Pisón S, Varea Calderón V. Autoimmune hepatitis in pediatric patients . Rev Esp Enferm Dig 2007; 99: 255-258.

INTRODUCTION

Autoimmune hepatitis (AIH) is an inflammatory liver illness of unknown origin. It causes a progressive destruction of hepatic parenchyma, and develops into cirrhosis and liver failure if immunosuppressive treatment is not initiated early.

Received: 03-07-06.
Accepted: 25-01-07.

Correspondence: Ruth García Romero. Paseo Fabra y Puig, 115-123, esc. dcha. Sobreático 2ª. 08016 Barcelona. e-mail: ruthgarciaromero@yahoo.es

The pathogenesis is governed by an immunoregulation disturbance in which individual genetic susceptibility plays a role (1,2); this brings about the production of antibodies in response to hepatocellular antigens. These antibodies serve as markers of disease (3), although their pathogenic role and their value for follow-up evaluation remain controversial. In terms of serological profile they are classified as either type-I AIH, positive for antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), or both, or type-II AIH, positive for liver-kidney anti-microsome antibodies (LKM-1) (4). Type II usually offers a poorer prognosis in that it evolves more quickly toward cirrhosis, and also frequently presents as fulminant hepatitis, above all in young infants (5,6).

AIH is more frequent in women (type I 75% and type II 95%), and is associated with hypergammaglobulinemia and autoimmune illnesses in patients or their relatives. It is associated with HLA A1/B8/DR3 and DR4Se haplotypes. AIH rarely presents earlier than two years of age, but from this point onwards its frequency increases and incidence peaks at 10 to 30 years of age (7).

The disease manifests in various ways (8): asymptomatically, with changes in laboratory parameters, with symptoms similar to those of acute viral hepatitis, or with the pattern of progressive liver insufficiency culminating in cases of fulminant hepatitis with liver failure (9). This last clinical form is more common among the young population than it is among adults.

The most frequent laboratory findings are hypertransaminasemia and hypergammaglobulinemia. Pathology does not reveal unique histological characteristics; rather, it is usually similar to chronic hepatitis, with presence of periportal necrosis and lympho-plasmocytic infiltration. The formation of hepatocytic rosettes is typical (10). In advanced cases nodular regeneration and/or fibrosis may be seen.

The main therapeutic strategy is aimed at modifying the natural evolution of the disease, since only rarely does a patient with AIH go into remission. The goals of treatment are to relieve symptomology, improve biochemical parameters, reduce inflammatory components and liver tissue fibrosis, prevent the evolution of chronic hepatitis into cirrhosis, and –most critical– reduce mortality. Immunosuppressive treatment inhibits the inflammatory response, but does not correct the primary immunomodulating disorder, so relapses are frequent when treatment is withdrawn. Corticosteroids, often in combination with azathioprine, constitute the treatment of choice to both bring about and then maintain remission (11-14). Other immunosuppressants such as cyclosporine (15,16), tacrolimus (17), and mycophenolate mofetil (18,19) may be indicated in cases in which response is poor to classical treatment (20), or in which classical treatment induces adverse side effects (21). At present there is no widely accepted criterion regarding the optimal length of treatment in pediatric patients.

The aim of our study was to evaluate the clinical, laboratory, and histological characteristics, as well as response to treatment and evolution, of pediatric patients diagnosed with and treated for autoimmune hepatitis I and II in our hospital during the past ten years.

PATIENTS AND METHODS

We carried out a retrospective study (January 1995 to December 2005) of patients diagnosed with AIH in the Service of Pediatric Gastroenterology at Hospital Sant Joan de Déu, Barcelona, Spain. The diagnosis of AIH was established in accord with guidelines laid out by the International Autoimmune Hepatitis Group, published in 1993 (22) and revised in 1999 (23) (Table I). The variables analyzed in our study were: age, sex, form of clinical presentation at diagnosis, biochemical parameters of liver function (aminotransferases, bilirubin, gamma-glutamyl-transpeptidase, alkaline phosphatase, prothrombin activity, proteins, and albumin), serum immunoglobulin levels, autoimmunity markers, histology, treatment, need for liver transplant, clinical evolution, and association with other autoimmune diseases in the patient and immediate relatives. Viral serology for hepatitis A, B, C, herpes virus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) was systematically carried out and proved negative in all cases. Also ruled out were Wilson's disease, alpha-1-antitrypsin deficiency, hemosiderosis, and other genetically-based diseases, as well as

Table I. AIH International Diagnostic Group 1999 score

Parameters	*Score*
– Female sex	+2
– FA/AST (> 3 y 1,5)	-2/+2
– IGG (g/l) > 20/15-20/10-15/< 10	+3/+2/+1/0
– ANA, ASMA o ALKM-1 > 1/80, 1/80, 1/40, < 1/40	+3/+2/+1/0
– Other auto Abs	+2
– AMA +	-4
– Viral hepatitis markers (1) yes/no	-3/+3
– Hepatotoxic medications yes/no	-4/+1
– Transfusion yes/no	-2/+1
– Alcohol < 25 g/day > 60 g/day	+2/-1
– Associated autoimmunity	+2
– Histopathology	
Lobular hepatitis/Bridge necrosis/ Rosettes or lympho-plasma cel linfiltrate	+3/+2/+1
Biliary lesions/No lesions	-3/-5
– HLA: B8-DR3 o DR4	+1
– Response to treatment	
Complete/partial	+2/0
No response/Relapse without treatment	-2/+3
Cumulative diagnostic score	
– PRE-treatment Definitive AIH/Likely AIH	> 15/ 10-5
– POST-treatment Definitive AIH/Likely AIH	> 17/ 12-7

(1) Viral hepatitis markers for A, B and C, CMV and VEB.

potential hepatoxic conditions. For cholestatic forms sclerosing cholangitis was ruled out within the autoimmune group. Following confirmation of diagnosis forms of clinical presentation were analyzed: acute (symptoms similar to those of acute viral hepatitis), chronic (asthenia, anorexia, ascites, enlarged liver, enlarged spleen, and jaundice), and fulminant hepatitis. They were classified according to the presence of positive antibodies into type I (ANA and/or ASMA) and type II (anti-LKM-1). Liver biopsies were analyzed using conventional methods.

Medical treatment was established with azathioprine 1-2 mg/kg/day, maximum 100 mg/day, and corticoids 1-2 mg/kg/day, maximum 60 mg/day, with doses decreasing after 4-6 weeks while maintaining the minimum dose necessary to keep histolysis enzymes within the normal range.

RESULTS

In the last ten years 7 patients were diagnosed with AIH in our center. Females predominate among patients, with 5 girls (71.5%) and 2 boys (28.5%). Age at diagnosis ranged from 21 months to 12 years and 9 months, for an average age of 7 years and 7 months. Five patients (2 boys and 3 girls) were diagnosed with type-I AIH, and two (girls) with type-II AIH.

The most frequent clinical presentation for type-I AIH was in the form of acute hepatitis in 3 cases, 2 of which also showed signs of cholestasis; in the other two patients presentation was progressive hepatic insufficiency. The 2 patients with type-II AIH were identified following a laboratory work-up, as they were both asymptomatic at diagnosis.

Liver function data showed severe cytolysis with increased serum transaminase levels to ten times their normal values in 71.5% of our series.

Hypergammaglobulinemia was observed in 85% of cases. The values of each patient's biochemical parameters are listed in table II. Histopathological findings revealed chronic hepatitis in 5 patients (71.5%), one of whom showed signs of cirrhosis. In 3 patients (42.8%) there was evidence of confluent necrosis, and in 5 patients of lympho-plasmocytic infiltration (Table III).

One patient had insulin-dependent diabetes mellitus diagnosed two years prior to the diagnosis with AIH. The patient's mother in turn had vitiligo. None of the remaining cases showed an association with any autoimmune disease, however. The medication indicated at diagnosis for all patients was azathioprine and prednisone, with the exception of one girl with mild hepatic inflammation who was treated with prednisone alone, and whose liver function progressively returned to normal. At present 3 patients continue to be treated with azathioprine and steroids, while two are on azathioprine monotherapy. One of the patients with chronic hepatitis developed fulminant hepatitis with hepatic encephalopathy during the course of treatment; a liver transplant was therefore indicated. The patient's histopathology already included a pattern of liver cirrhosis at diagnosis.

Clinical remission was observed in patients with clinical hepatitis as jaundice clearance and overall improved symptomatology. Biochemical remission was seen as the normalization o liver function parameters in an average time frame of 14 months (range 1.5-36 months). Two patients (28.5%) relapsed upon steroids withdrawal. Currently, one of them continues to require a minimal quantity of prednisone eight years after treatment onset for her illness (type-II AIH). None of the patients in our series has died.

DISCUSSION

Although autoimmune hepatitis remains an infrequent illness among pediatric patients, it is an important cause of chronic liver disease in this age group. Our series of patients is limited, but we may safely draw some conclusions from the results obtained. The predominance of females among sufferers, widely documented in the published literature, has been borne out in our sample as well (24). The forms of presentation are varied, ranging from asymptomatic cases to situations of acute liver failure, and they may be indistinguishable from acute viral hepatitis (25). In our series there were no significant differences in this regard, although we did observe that type-II AIH cases were accidental findings in the course of routine analysis, as patients were asymptomatic at diagnosis. Intense cytolysis (aminotransferases 10 times their normal level) and hypergammaglubulinemia were seen in

Table II. Clinical lab characteristics of patients in the study

Patient	*Age (years)*	*Sex*	*Clinical status*[1]	*ALT. AST x normal value*	*TP%*	*Bilirubin (mg/dl)*	*IGG*[2] *(mg/dl)*	*AIH type*	*ASMA*	*ALKM*	*Associated autoimmune*
1	3.6	Female	Acute	x20	60	5.2	1807	1	1/160	-	-
2	10	Female	Laboratory	x10	68	0.9	1900	2	-	1/160	-
3	1.9	Male	Acute	x40	65	12.7	1137	1	1/80	-	-
4	8	Female	Laboratory	x10	92	0.7	2765	2	-	1/640	-
5	6	Female	Acute	x5	85	0.8	1450	1	1/80	-	DM I
6	12.9	Male	Chronic	x5	20	3.6	5757	1	1/160	-	-
7	12	Female	Chronic	x50	67	3.3	2970	1	1/640	-	-

[1]Clinical status: acute (acute hepatitis), chronic (progressive liver failure), laboratory (asymptomatic lab findings). [2]Normal IGG range < 1,300 mg/dl.

Table III. Pathological characteristics of liver biopsies

Patient	*Histopathology*
1	Portal fibrosis with bridges
	Necrosis in punch biopsy
2	Lympho-plasmocytic infiltration
3	Lympho-plasmocytic infiltration, necrosis
4	Portal fibrosis
	Focal necrosis
5	Portal fibrosis
	Lympho-plasmocytic infiltration
6	Cirrhosis
	Lympho-plasmocytic infiltration
7	Portal fibrosis
	Lympho-plasmocytic infiltration

practically all patients in our series. Presence of autoimmune disease is a frequent occurrence in this pathology, and represented 14% of our sample. The high percentage of response to medication (85.5% of the patients) leads to conclude that early diagnosis and treatment are very important, as the aim is to prevent progression to chronic hepatitis and cirrhosis. Immunosuppressive treatment discontinuation in children correlates with a high level of relapse, as we have noted to be the case among our patients; even though the length of treatment is not well established (26), it should continue until remission is documented both histopathologically and using clinical labs. The high mortality seen in some studies (27,28) was not seen in our study, although one patient did require an emergency liver transplant because of acute liver failure.

No controlled studies have been carried out in children, so the decision on when to withdraw medication must be made on a case-by-case basis, with long-term follow-up monitoring of liver function.

REFERENCES

1. Pando M, Larriba J, Fernández GC, Fainboim H, Ciocca M, Ramonet M, et al. Pediatric and adult forms of type 1 autoimmune hepatitis in Argentina: evidence for differential genetic predisposition. Hepatology 1999; 30: 1374-80.
2. Donaldson PT, Doherty DG, Hayllar KM, McFarlane IG, Johnson PJ, Williams R. Susceptibility in autoimmune chronic active hepatitis human leucocyte antigens DR 4 and A1-B8-DR3 are independent risk factors. Hepatology 1991; 13: 701-6.
3. García Novo MD, Acuña D, Martinez Gómez J, Pedron C, Martínez Pérez A, Vicente Prada I, et al. Hepatitis autoinmune. Revisión de una serie de 11 casos pediátricos. An Esp Pediatr 2001; 54: 21-5.
4. Homberg JC, Abuaf N, Bernard O, Islam S, Álvarez F, Khalil SH, et al. Chronic active hepatitis associated with anti liver-kidney microsoma antibody type: A second type of "autoimmune" hepatitis. Hepatology 1987; 7: 1333-9.
5. Maggiore G, Porta G, Bernard O, Hadchouel M, Álvarez F, Homberg JC, et al. Autoimmune hepatitis with initial presentation as hepatic failure in young children. J Pediatr 1990; 116: 280-2.
6. Porta G, Gayotto LC, Álvarez F. Anti liver kidney microsoma antibody positive autoimmune hepatitis presenting as fulminant liver failure. J Pediatr Gastroenterol Nutr 1990; 11: 138-40.
7. Vento S, Garofano T, Di Perri G, Dolci L, Cocia E, Basseti D. Identification of hepatitis A virus as a trigger for autoimmune chronic hepatitis type 1 in susceptible individuals. Lancet 1991; 337: 1183-7.
8. Prados J, Antonaya M, Del Rey V, Urruzuno P, Medina E, Carbajo AJ, et al. Hepatitis autoinmune. Análisis de una serie pediátrica. An Esp Pediatr 2001; 54: 17-20.
9. Maggiore G, Veber F, Bermard O, Hadchouel M, Homberg JC, Alvarez F, et al. Autoimmune hepatitis associated with anti-actin antibodies in children and adolescents. J Pediatr Gastroenterol Nutr 1993; 17: 376-81.
10. Maggiore G, Bernard O, Homberg JC, Hadchouel M, Álvarez F, Hadchouel P, et al. Liver disease associated with anti-liver-kidney microsome antibody in children. J Pediatr 1986; 108: 399-404.
11. Krawitt EL. Autoimmune hepatitis. N Engl J Med 1996; 334: 897-903.
12. Obermayer-Straub P, Strassburg ChP, Manns MP. Autoimmune hepatitis. J Hepatol 2000; 32: 181-97.
13. Vergani D. LKM antibody: getting in some target practice. Gut 2000; 46: 449-50.
14. Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. N Engl J Med 1995; 333: 958-63.
15. Hyams JS, Ballow M, Leichtner AM. Cyclosporine treatment of autimmune chronic active hepatitis. Gastroenterology 1987; 93: 890-3.
16. Debray D, Maggiore G, Girardet JP, Mallet E, Bernard O. Efficacy of cyclosporin A in children with type 2 autoimmune hepatitis. J Pediatr 1999; 135: 111-4.
17. Van Thiel DH, Wright H, Carroll P, Abu-Elmagd K, Rodríguez-Rilo H, McMichael J, et al. Tacrolimus: a potential new treatment for autoimmune chronic hepatitis: results of an open-label preliminary trial. Am J Gastroenterol 1995; 90: 771-6.
18. Dhavan A, Mieli-Vergani G. Mycophenolate mofetil: - a new treatment for autoimmune hepatitis? J Hepatol 2000; 33: 480-1.
19. Jackson LD, Song E. Cyclosporin in the treatment of corticosteroid-resistant autoimmune chronic active hepatitis. Gut 1995; 36: 459-61.
20. Sherman KE, Narkewicz M, Pinto PC. Cyclosporine in the management of corticosteroid-resistant type I autoimmune chronic active hepatitis. J Hepatol 1994; 21: 1040-7.
21. Richardson PD, James PD, Ryder SD. Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis in patients resistant to or intolerant of azathioprine. J Hepatol 2000; 33: 371-5.
22. Johnson PJ, McFarlane IG. Meeting report: International autoimmune hepatitis group. Hepatology 1993; 18: 998-1005.
23. Álvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International autoimmune hepatitis group report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999; 31: 929-38.
24. Krawitt EL. Autoimmune hepatitis. N England J Med 2006; 354: 54-66.
25. Codoner-Franch P, Bernard O, Maggiore G, Alagille D, Álvarez F. Clinical and immunological heterogeneity of anti-liver-kidney microsome antibody-positive autoimmune hepatitis in children. J Pediatr Gastroenterol Nutr 1989; 9: 436-40.
26. Ferreira AR, Roquete ML, Penna FJ, Toppa NH, De Castro LP. Type 1 autoimmune hepatitis in children and adolescents: assessment of immunosuppressive treatment withdrawal. J Pediatr (Rio J) 2005; 81: 343-8.
27. Roberts SK, Therneau TM, Czaja AJ. Prognosis of histological cirrhosis in type 1 autoimmune hepatitis. Gastroenterology 1996; 110: 848-57.
28. Cotler SJ, Jakate S, Jensen DM. Resolution of cirrhosis in autoimmune hepatitis with corticosteroid therapy in autoimmune hepatitis. J Clin Gastroenterol 2001; 32: 428-30.