Immunological disorders: (Type 1 Diabetes, Idiopathic Thrombocytopenic Purpura and Hashimoto Encephalopathy), Associated with Autoimmune Hepatitis

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Abstract

Autoimmune hepatitis (AIH) is a liver disease that runs a course of chronic and progressive inflammation. This occurs in young children and adolescents. AIH can also be manifested in an acute and aggressive form. Its etiology is unknown. Two varieties have been reported. These are autoimmune hepatitis type 1 (AIH-1) and type 2 (AIH-2). AIH-1 affects children as well as adults and it is related with the presence of antinuclear (ANA) and anti-smooth muscle (ASM) antibodies. AIH-1 is associated with immunological illnesses such as ulcerative colitis, sclerosing cholangitis, arthritis, and vasculitis. AIH-2 is more frequent in children. It presents with liver and kidney microsome (Anti-LKM-1) antibodies and anti- cytosal antibodies (Anti-LC-1). AIH-2 has also been associated with other immunopathies such as polyendocrinopathy, vitiligo, thyroiditis, alopecia and diabetes mellitus type 1 (DM1). This report describes the clinical course of two patients with AIH: a female treated since five years of age and followed during 18 years. After 11 years, the patient developed DM1 and later anorexia nervosa. This patient died due to complications of the later. The other patient, who was diagnosed with AIH at the age of 10 years, was treated and followed during 10 years. This patient manifested idiopathic thrombocytopenia purpura (ITP) and Hashimoto encephalopathy during the course of the disease. This patient continues to remain under control. The relationship of AIH-1 with other autoimmune processes, such as Diabetes mellitus type 1 (DM1) until now, has been poorly investigated. Also, ITP followed by Hashimoto encephalopathy was a rare association in our patient. It has been considered that these are a consequence of autoimmune dysregulation.

Key Words:
Autoimmune hepatitis in children; Diabetes mellitus type 1; Thrombocytopenic purpura; Hashimoto encephalopathy.

Background

Autoimmune hepatitis (AIH) is a liver disease that entails chronic and progressive inflammation and its etiology is unknown to date. There are studies currently trying to identify the genetic factors and markers of the risks of the disease occurring in populations of the world [1,2]. The following two types of these diseases are distinguished by clinical course and serological findings in Autoimmune hepatitis type 1 (AIH-1) and type 2 (AIH-2) [1,2]. Both are characterized by the presence of autoantibodies in addition to high levels of immunoglobulin G (IgG) and low levels of circulating complementary factor 4a (C4a) and immunoglobulin A (IgA). Findings of hepatitis and the infiltration of plasma cells within the portal system were identified by histopathology [1-5].

The course of the disease occurring in young children and adolescents tends to be acute and aggressive or fluctuations of spontaneous remission periods [6-8]. The laboratory results express themselves as autoimmunity markers for AIH-1 within the following: the presence of antibodies in serum; anti-smooth muscle (ASM); anti-actin and/or anti-nuclear (ANA) antibodies. Also, anti-soluble liver antigen (SLA) antibodies are found associated with immunological illnesses such as ulcerative colitis, Crohn’s disease, hemolytic anemia, thrombocytopenia, glomerulonephritis, fibrosing alveolitis, sclerosing cholangitis, arthritis, and vasculitis.

In AIH-2, we find liver and kidney anti-microsome (LKM1) and/or Liver anti-Cytosal type 1, associated with others such as autoimmune enteropathy, polyendocrinopathy, vitiligo, ectodermal dystrophy, lymphoproliferative syndrome, candidiasis, thyroiditis, alopecia, and DM1 [1,2,5-8]. Recently, AIH-1 and AIH-2, also have been associated with celiac disease [9].

When diagnosing pediatric patients other diseases should be considered within the differential diagnosis. These include acute or chronic viral hepatitis, metabolic disorders and toxic agents that lead to liver damage. The mechanism of liver damage is associated with immune reactions against hepatic antigens not adequately controlled by regulatory T cells [10].

The majority of patients respond favorably to immunosuppressive treatment. Prednisone and azathioprine are drugs used in AIH, however, such medications such as: calcineurin inhibitors (cyclosporine and tracolimus), rapamycin, mycophenolate mofetil, deflazacort, budesonide, ursoeodeoxyacetic acid, and cyclofosfamide are also used. More recently, molecular interventions are performed by the feasibility of using anti-CD3 non-mitogenic antibodies, anti-CD20 monoclonal antibodies, anti-tumor necrosis factor-alpha (TNF)-alpha antibodies, etanercept, recombinant interleukin, and antigen-4 (recombinant) T-cytotoxic lymphocytes, fused with immunoglobulins,
all of these with limited experience are included in other autoimmune processes [10] and, depending on the treatment response, the biochemical clinical remission that can be achieved is histological after various years [11]. However, even after treatment, the disease progresses with liver destruction and making transplantation necessary [1,2,5-7]. The mechanisms of genetic factors and associated autoimmune diseases illnesses are only partially understood to date [4-6]. In this report, we present two pediatric patients who manifested associated autoimmune diseases related to AIH type 1.

Objective

The aim of this report is to describe the basic clinical, laboratory an histological features of AIH and the clinical course of two patients with AIH-1 who developed diabetes mellitus type 1 (DM1), idiopathic thrombocytopenia purpura (ITP) and Hashimoto encephalopathy.

Patients and Methods

Description of the patient’s clinical course, features and results

Patient 1: Twenty-three year-old female, family history: Negative for diabetes, a brother with thyroiditis and idiopathic thrombocytopenic purpura (ITP), a sister with vitiligo, and another with dermatomyositis.

The patient was seen for the first time at the age of five with symptoms of hyporexia, abdominal pain, and minimal ictericia. She was clinically and biochemically diagnosed with hepatitis. However, because the latter presented without ictericia and with persistence of transaminases, the possibility was proposed of autoimmune hepatitis, and immunological studies, and a percutaneous (p.c.) liver biopsy were performed. The results of the liver tissue histopathology revealed the presence of lympho-plasmocytic infiltrate, macrophages, and plasma cells. In the portal space, liver lobe necrotic foci, rupture of the portal space adjacent to the limiting plate, and inflammatory infiltrate extending to the hepatic parenchyma were identified (Figure 1A).

Figure 1: Hepatic parenchyma.

From these results, the diagnosis of AIH-1 was established and the treatment was initiated with prednisone at a dose of 2 mg/kg of BW, which was administered during 10 months, with gradual reductions to 0.5 mg/kg of BW, daily and later, every other day. In 1993, after a liver control biopsy and biochemical and histological data of activity, azathioprine was added to the course of treatment at a dose of 2 mg/kg of BW, in addition to prednisone at 1 mg/kg of BW (Figure 1B).

The patient was treated during 18 years, from January 1992 to April 2010. In 2002, the patient presented with recurrent episodes of cough with bronchitis and bronchospasm. The patient also presented with four episodes of maxillary sinusitis which were treated by an allergologist and pneumologist. During the first week of January 2004, the patient manifested polyuria, polydipsia, hyporexia, and weight loss. A glycemia study revealed 386 mg/dl of glucose and marked glycosuria in urine, establishing a diagnosis of diabetes mellitus type 1 (DM1). At this time a treatment with neutral protamine Hagedorn (NPH)-based insulin at a rate of 0.5 U/kg of BW, in two daily applications subcutaneously (sc) was initiated and a good control of glucose levels was present until 2008.

Within the lapse of 18 years, p.c. liver control biopsies were performed and follow-up and diagnostic studies were conducted. These included blood chemistry, bilirubin, ALT, AST, AP, GGTP, platelets, prothrombin time PT, partial thromboplastin time PTT and Normalized International Index (INR), serological tests for hepatitis A, B, and C. Also serum electrolytes, purified protein derivative (PPD), and coccidioidin tests, serum ammonium, anti-DNA antibodies, protein electrophoresis, serum immunoglobulins, anti-mitochondrial antibodies, (ASM), (SLA), (LKM1), LE cells, antitrypsin alpha 1, ceruloplasmin, thyroid function tests, creatinine depuration, anti-endomysial antibodies, anti-gliadin antibodies, anti-transglutaminase antibodies, anti-glutamate decarboxylase (GADA) 65, peptide C, CD4, and glycosylated Hemoglobin (HB), in addition to skin tests for allergy, and ultrasound (US). The positive tests are show in Table 1.

Table 1: Relevant laboratory test in case 1.

<table>
<thead>
<tr>
<th>Test</th>
<th>First results</th>
<th>Last results</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>304 U/L</td>
<td>34 U/L</td>
<td>Several test, until normality</td>
</tr>
<tr>
<td>AST</td>
<td>324 U/L</td>
<td>24 U/L</td>
<td></td>
</tr>
<tr>
<td>GGTP</td>
<td>120 U/L</td>
<td>70 U/L</td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>1:140</td>
<td>1:10</td>
<td></td>
</tr>
<tr>
<td>ASM</td>
<td>1:80</td>
<td>1:10</td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>2.3 m/dL</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Anti-glutamate decarboxylase antibodies 65(GADA)</td>
<td>Positive</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>C peptide</td>
<td>2.9 mg/ml</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Glycosylated hemoglobin</td>
<td>7.4–10.0</td>
<td>-</td>
<td>Several test between normality</td>
</tr>
<tr>
<td>Skin test for allergy</td>
<td>Positive to plant pollen</td>
<td>-</td>
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In 2005, after a p.c. liver biopsy demonstrated normal hepatic tissue. Liver function tests were performed during the next three consecutive years. Considering normal biochemical and histological disease remission criteria, the treatment with prednisone and...
azathioprine was withdrawn and continued only with (NPH)-based insulin.

In November 2008, the patient presented emotional disorders and changes in her behavioral patterns. In addition to progressive weight loss reaching malnutrition, anorexia nervosa was diagnosed. The insulin requirement for glycemic control was reduced. The patient did not present alterations in liver tests, from 2008 and 2010. The patient’s physical deterioration was progressive. In February 2010, the patient developed pneumonia, which was treated. In April, the patient had a relapse of the pneumonia and died.

**Patient 2:** Nineteen year-old male. Family history: negative for autoimmune and oncological-hematological diseases. At the age of three, hvery history of viral hepatitis. In 2003, at the age of 10, the patient presented with hepatalgia without icteric or choluria. The liver was found to be 3.5-3.3 on physical exploration.

Laboratory tests were negative for serological markers for hepatitis A, B, and C. Other studies obtained included: blood chemistry, triglycerides, TP, TTP, INR, total proteins, protein electrophoresis, general urine examination, a ALT, AST, AP, GGTP, ceruloplasmin, Alpha 1-antitrypsin, Ac-Anti-mitochondrial, Ac-ASM and hepatic triglycerides, TP, TTP, INR, total proteins, protein electrophoresis, ultrasound (US) study. The positive laboratory tests are seen in Table 2.

The (p.c.) liver biopsy was performed. The histopathological findings included the presence of lymphocytic infiltrate in the plasmocytic lymphocyte portal space, macrophages, and plasma cells, which invade the hepatic lobule, with infiltrate and hepatocyte destruction within the lobule’s periphery, and with rupture of the limiting plate, establishing the diagnosis of autoimmune hepatitis type 1 (AIH-1). Treatment was initiated in 2003, with 25 mg daily prednisone and 50 mg daily azathioprine. From 2004 to 2007, the patient’s liver function tests were within normal limits.

In March 2007, a platelet count of 121,000 × mm$^3$ was seen for the first time. There were no clinical manifestations of bleeding. Platelet controls improved with an adjustment in the prednisone dose, which had been reduced to 10 mg every day due to steroidal effects (Cushing signs). From 2007 to 2010, the patient was stable. In 2010 a leukopenia of 2,528 × mm$^3$ was present and azathioprine was reduced to a 12.5 mg daily and prednisone reduced to 10 mg daily.

### Table 2: Relevant laboratory test in case 2.

During 2011, the platelet count vacillated between 50,000 at 85,500, TP 16, and INR, 1.4, and the oral dose of prednisone was increased to 100 mg/daily for 4 days and reduced to 50 mg on subsequent days. The patient’s platelets remained stable for 6 months. The oral administration of prednisone was continued at 4 mg/kg of BW, and afterward, at 10 mg /daily. Azathioprine was reduced to 12.5 mg /daily. A new depleted count of platelets in august 2011 and a bone marrow examination was performed to evaluate for thrombocytopenia associated with the use of immune-suppressors and the possibility was also of AIH-related thrombocytopenia. Anti-platelet antibodies were positive in >47% (Anti-GPIA/IIA). An assessment was requested by the hematologist, who decided to increase the dose of prednisone. The patient persisted with thrombocytopenia until 2012, and treatment was changed to romiplostim, 2 mcg/kb of BW biweekly. Platelets increased after each treatment, but with sudden subsequent rapid platelet decrease. In February 2012, a (p.c.) liver biopsy revealed marked autoimmune-process activity. Pre-cirrhotic changes were not observed (Figure 2A and 2B).
Azathioprine withdrawal and mycophenolate mofetil was initiated, because a bone marrow study was requested due to considering thrombocytopenia associated with the use of immunosuppresses, the Anti-platelet antibodies were positive in >47% (Anti-GPIA/IIA).

The controls of the ASM positive 1:20, ANA, and anti-microsomal antibodies positive 1:40, platelets 80,000 × mm³ were obtained. In July 2013, mycophenolate mofetil was withdrawn, because not observe changes to improvement and treatment with azathioprine and prednisone was instituted.

In October of 2014, the patient presented with stereotyped and repetitive movements of both hands, dismetry, irritability, disorder of behavior, insomnia and ataxia. Laboratory results for hemoglobin, leucocytes sodium, potassium calcium, magnese, C3, C4, Epstein Barr virus antibodies, Cryptococcus neoformans Ag, Heplex simplex I-II Antibodies, Citomegalovirus antibodies, VDRL, all were negative or normal; aminotransferases and ammonia were normal (Table 2).

The electroencephalogram was normal. Psychiatric consultation of patient’s behavior disorders crisis recommended treatment with haloperidol and clonazepam; after a neurologist consultant, recommended gadolinion a magnetic resonance imaging (BMI) of the brain. The examination revealed T2 symmetric and bilateral areas with high signal present within the basal ganglia, thalamus partially with extension into the mesencephalon, pons, and other areas of the encephalon with alterations (Figure 3).

With the diagnosis of Hashimoto encephalopathy, we used treatment with metil-prednisolone at dose of 1 gram intravenous, each 24 hours during 5 days followed by prednisone oral at dose of 60 mg/day, plus 25 mcg/day of thyroxin. After the first month the patient demonstrate neurological improvement. The irritability and behavior disorders disappeared and the stereotypic movements also improved. However, the ataxic signs still persisted.

Until December of 2014, there were variations of the laboratory results. There were normal to low increases of transaminases and the platelets vacillated between 25,000 and 80,000 × mm³. Azathioprine and prednisone were employed in the treatment.

### Discussion

In pediatric ages, as in adults, the clinical variants of AIH have been associated with other autoimmune illnesses. AIH-1 is seen in ulcerative colitis, Crohn’s disease, thrombocytopenia, hemolytic anemia, glomerulonephritis, fibrosing alveolitis, sclerosing cholangitis, arthritis, and vasculitis. In contrast, AIH-2 has been associated with autoimmune enteropathy, polyendocrinopathy, vitiligo, ectodermal dystrophy, the autoimmune lymphoproliferative syndrome, candidiasis, thyroiditis, alopecia, and DM1. In some types of AIH, celiac disease is present [2,3,9]. It is also known that these extra-intestinal illnesses can be present in 40% of patients and in 35% of direct-line relatives. This occurred in the patient of case 1, with AIH-1, who developed DM1 with positive specific markers such as anti-glutamate descarboxylase antibodies (GADA) 65. The patient is 1; had familial antecedent of autoimmune diseases in three siblings: autoimmune thyroiditis, ITP, dermatomyositis, vitiligo. The results of recent genetic studies [4,5] support the possibility of complex genetic disorders, because of the presence of genotypes, such as the antigens of the histocompatibility complex (HLA-DRB1*0301 and HLA DRBB1*0401) reinforce the role of human leukocyte antigens (HLA) in the pathogenesis and the strong genetic risk for having AIH. With regard to DM1, it has been considered that there exists autoimmune dysregulation of its genesis, in which LKM1 antibodies participate, directed against cytochrome P4502D6 (CYP2D6) and an enzyme expressed by carboxypeptidase H (CPH) hepatocytes, which become a molecular target in DM1, sharing similarity for the second major LKM in epitope CYP2D6 and sharing modified amino acids motif with CPH. This suggests that autoimmunity to tissue-specific autoantigens may involve other organs, expressing proteins that share similarity to the initial autoantigen by means of a cross mechanism and may lead to the clinical manifestation as an autoimmune disease in individuals susceptible forANA and SMA characteristic of AIH-1. This particularity has been limitedly studied in adults and in children [2,15]. Its presence has been persistently related with AIH-2. It is probable that, at least in the pediatric ages, DM1 is also present in AIH-1, as it has been recently reported but poorly investigated [5,12]. On the other hand, there is also a relationship among patients with DM1 with celiac disease and AIH-1 [9], and its existence is probably not rare in a greater number of individuals with these associations. In this patient, serological markers for celiac disease were negative. On the other hand, the patient of case 1, also developed asthmatic-type symptoms. While it is true that there were positive tests for specific allergens, we must remember that this illness also possesses a hereditary factor and an immunological background.

This patient, after 13 years of treatment, showed the clinical, biochemical, and histological criteria to consider the remission of AIH; thus continuing only with the use of insulin, maintaining acceptable control of the patient’s DM1. Unfortunately, between December 2007 and April 2010, this patient presented behavioral changes, developed anorexia nervosa, which led to severe malnutrition and recurrent infections, and finally died. With regard to the relationship between the anorexia and AIH, solely the inverse has been described. Severe anorexic status can lead to liver damage that becomes evident due to the rise in transaminases, but the relationship, to date, has not been described with autoimmune phenomena [14,15].

Thrombocytopenia is very common in advanced liver disease and is present in up to 85% of patients with cirrhosis which increases the risk of bleeding. The incidence of thrombocytopenia as an autoimmune phenomenon, has been reported in patients with AIH, it is not seen
frequently in the medical literature. The initial mechanisms that intervene in the presence of autoimmune idiopathic thrombocytopenic purpura (ITP) have not been identified. 80% of cases are primary and in 20% and are considered to be associated with other pathologies. This classification, although practical, is subject to modifications in the face of novel etiologies or associated conditions, giving rise to the reclassification of secondary cases. Within the origin of ITP, an immunological stimulus that can occur during some infections can instigate a break in platelet tolerance. It can also cause immunological abnormalities that immediately occur that is conveniently explained in the following manner: the immune dysregulation that follows ITP is becoming clearer. In addition to antiplatelet a Ab-mediated clearance of platelets. Abs also may fix complement to platelets, T-cells, and cytokines, generating a type 1 immune response, and the monocyte-phagocyte system appears to be more active [16,17]. Thus, the attack on platelets and megakaryocytes is propagated on multiple fronts. In addition, the genetic predisposition of the individual permits the development of ITP [16,17]. In this second case, in the adolescent with AIH-1 who developed thrombocytopenia, at the beginning it was considered that the latter was associated with the use of azathioprine. The bone marrow study reported discrete cellular depression and diminished megakaryocytes. Since AIH did not respond to Azathioprine, and due to the possibility that this drug could induce bone marrow hypoplasia, it was decided to withdraw this medication and to begin the purine antagonist, mycophenolate mofetil, which has been recommended in these cases [18,19] and increase the Prednisone dose. Our hematologist concluded that the thrombocytopenia was caused by the disruption of the AIH-related immune. We decided to start treatment with romiplostim, a thrombopoietin-stimulating pharmaceutical. The response to the drug was not as expected. The patient continued to have thrombocytopenia, as well as notable AIH activity.

HE is characterized by various neuropsychological symptoms which include: cognition and/or consciousness deterioration, personality changes, seizures and myoclonus. Recently, this entity has attracted complement to platelets, T-cells, and cytokines, generating a type 1 immune response, and the monocyte-phagocyte system appears to be more active [16,17]. Thus, the attack on platelets and megakaryocytes is propagated on multiple fronts. In addition, the genetic predisposition of the individual permits the development of ITP [16,17]. In this second case, in the adolescent with AIH-1 who developed thrombocytopenia, at the beginning it was considered that the latter was associated with the use of azathioprine. The bone marrow study reported discrete cellular depression and diminished megakaryocytes. Since AIH did not respond to Azathioprine, and due to the possibility that this drug could induce bone marrow hypoplasia, it was decided to withdraw this medication and to begin the purine antagonist, mycophenolate mofetil, which has been recommended in these cases [18,19] and increase the Prednisone dose. Our hematologist concluded that the thrombocytopenia was caused by the disruption of the AIH-related immune. We decided to start treatment with romiplostim, a thrombopoietin-stimulating pharmaceutical. The response to the drug was not as expected. The patient continued to have thrombocytopenia, as well as notable AIH activity.

Conclusions

Recent evidence increasingly reinforces a genetic correlation and the role of human leukocyte antigens (HLA) in its pathogenesis of AIH and in terms of the relationship with other autoimmune processes, such as those of diabetes mellitus type 1 (DM1) and ITP, and HE. It behooves us to broaden our knowledge relative of both types of AIH (AIH-1 and AIH-2) with diverse immune diseases. As of date, this has been poorly investigated.

Abbreviations

Abs: Antibodies; Anti LC-1: Anti-cytosol antibodies; GADA: Anti-Glutamat decarboxylase antibodies; Anti-LKM-1: Anti-microosomal antibodies for liver and kidney; ANA: Anti-nuclear antibodies; Anti-GPIA/IIA: Anti-platelet antibodies; SMA: Anti-Smooth-muscle antibodies; SLA: Anti-Soluble liver antigen antibodies; ATGA: Anti-Thyroglobulin antibodies; AMA: Anti-Microosomal antibodies; NTF-alpha: Anti-Tumor necrosis factor-alpha antibodies; AIH: Autoimmune hepatitis; ASLO: Antiestrptolysin; AIH-1: Autoimmune hepatitis type 1; AIH-2: Autoimmune hepatitis type 2; HE: Hashimoto’s Encephalopathy; CPRH: Carboxypeptidase H; C4a: Complementary Factor 4; CYP2D6: Cytochrome P4502D6; GGT: Gamma-glutamyl transpeptidase; HB: Hemoglobin; HLA-DRB1*0301 and HLA DRB1*0401: Histocompatibility complex antigens; ITP: Idiopathic thrombocytopenic purpura; IgA: Immunoglobulin A; IgG: Immunoglobulin G; MRI: Magnetic Resonance Imaging; Anti-CD20: Mononuclear antibodies; Anti-CD3: Non-mitogenic antibodies; INR: Normalized International Index; PT: Partial thromboplastin time; PC: Peptide C; PT: Prothrombin time; PPD: Purified protein derivative; Serological tests for hepatitis A, B, and C; TSH: Thyroid stimulating hormone; VDRL: Venereal Disease Research Laboratory.

References


