Association of autoimmune hepatitis and multiple sclerosis: a coincidence?

Associação de hepatite autoimune e esclerose múltipla: coincidência?

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Abstract
Autoimmune hepatitis is a chronic liver inflammation resulting from deregulation of immune tolerance mechanisms. Multiple sclerosis is also an inflammatory disease in which the insulating covers of nerve cells in the brain and spinal cord are damaged. Here we present a case of an 18 year old female with multiple sclerosis who was treated with glatiramer acetate and with interferon beta 1a. Seven months after initiating treatment, liver dysfunction occurred. Clinical and laboratory findings were suggestive of drug-induced hepatitis, which led to the discontinuation of treatment with interferon, with clinical improvement. However facing a new episode of acute hepatitis one year later, this time without interferon, she was subjected to a liver biopsy, and the analysis of autoantibodies was positive for smooth muscle antibodies. Given the diagnosis of autoimmune hepatitis she started therapy with prednisolone and azathioprine, with good clinical and analytical response. Moreover, the demyelinating lesions of multiple sclerosis ameliorated. This is one of the few cases that describe the association of autoimmune hepatitis with multiple sclerosis, and there is a chance both diseases have the same autoimmune inflammatory origin.

Key-words: Liver, inflammatory; interferon; corticosteroids.

Introduction
Autoimmune hepatitis (AIH) is a chronic liver inflammation of unknown cause that results from the combination of environmental factors, dysregulation of immune tolerance mechanisms and genetic predisposition. It consists in the immune reaction to T-cell antigens induced on the liver, leading to a progressive necroinflammatory and fibrotic process in the liver. It has an incidence of 1-2 / 100,000 inhabitants, and women are more affected than men, at a ratio of 3.6: 1. The onset is usually insidious, with nonspecific symptoms such as fatigue, jaundice, nausea, abdominal pain or arthralgia; however, the presentation is highly variable, ranging from an asymptomatic presentation to a severe acute onset. The diagnosis is based on histologic abnormalities, clinical and laboratory data, high levels of serum globulins and characteristic autoantibodies. There are criteria that define a diagnostic score, which can be calculated before and after treatment; a pretreatment score of 15 indicates “final AIH” with a sensitivity of 95% and specificity of 97%. The established treatment is prednisolone in monotherapy or in combination with azathioprine; these immunosuppressive regimens promote a clinical, analytical and histological improvement.

Multiple sclerosis (MS) is a chronic disease of the central nervous system, usually diagnosed in the second or third decade of life, more common among women (3:1). It is characterized by inflammation and damage to the insulation shield that surrounds nerve fibers (myelin), resulting in progressive neurological injury, and a number of debilitating symptoms. Among the forms of treatment we find corticosteroids, interferons (IFN) and copolymers (glatiramer acetate, COP-1). The association between AIH and MS has been studied and reported. Here we discuss this relationship in connection with a case.

Clinical case
Female patient, 18 years old, caucasian. History of multiple sclerosis, follow-up by the Neurology service, treated with glatiramer acetate, with poor therapeutic compliance. In May 2005 began therapy with interferon beta 1a, showing, seven months later, several outbreaks of transaminase elevation (AST 413 IU/L, ALT 722 IU/L, GGT 111 IU/L, total bilirubin 6.44 mg/dL, direct bilirubin 3.28 mg/dL) interpreted as drug toxicity, which led to the discontinuation of treatment with interferon. However, in April 2006 there was a new episode of acute hepatitis (AST 628 IU/L, ALT 1116 IU/L, GGT 111 IU/L, total bilirubin 4.69 mg/dL, direct bilirubin 2.7 mg/dL), when she was no longer medicated. Viral markers for hepatitis B and C were negative, the analytical profile of iron was normal, there was no increase in cholestatic enzymes or alpha 1 antitrypsin deficit. During patient follow-up by the Medicine/Hepatology service from May 2006, she was subjected to a liver biopsy, which revealed a liver structure altered by interface hepatitis process with extensive peri-venular ballooning degeneration confluence, without biliary lesions or granulomas. The autoantibodies were positive (1/20) only for smooth muscle antibodies (SMA). Given the diagnosis of AIH she started treatment with prednisolone in monotherapy or in combination with azathioprine; these immunosuppressive regimens promote a clinical, analytical and histological improvement.

Key-words: Fígado; inflamatório; interferão; corticoesteróides
by a immunomodulatory dysregulation (Th1 vs. Th2 and Th17), a spontaneous formation of autoantibodies (ANA, anti-dsDNS) and a direct imbalance of liver cytokines. Glatiramer acetate is reported to be well tolerated. It is a synthetic random copolymer of four amino acids and is antigenically similar to myelin basic protein. Recently, glatiramer acetate was suggested to induce autoimmune diseases, such as myasthenia gravis, autoimmune thyreoiditis, and there are published cases of AIH. Glatiramer acetate can induce T helper type 2 cells that cross-react with myelin basic protein, releasing cytokines like IL-4, IL-5 e IL-10 which therefore may enhance the production of autoantibodies and lead to induction of autoimmune diseases in genetically predisposed patients. In our case, the patient had a new hepatic flare after discontinuation of interferon but on treatment with glatiramer acetate, which does not exclude any possible degree of toxicity for this drug. However liver function stabilized after therapy for AIH. Therefore, it seems that AIH, whether pre-existing or drug induced, was the underlying cause of hepatitis in this patient.

The association between MS and other autoimmune diseases has been published, including thyroiditis, myasthenia gravis and rheumatoid arthritis. Although it is known that the prevalence of AIH seems to be about 10-fold higher in patients with MS than in general population, only a few cases have been described. In Table 1 are summarized some of these registers, the first of which being the case under discussion.

Although both conditions occur on a specific population (young adults predominantly female), its prevalence may be underestimated since the AIH can be asymptomatic.

Figure 1. Magnetica Ressonance Imaging 2006 – where were reported several demyelinating lesions of multiple features.

Figure 2. Magnetica Ressonance Imaging 2012 – after the treatment of the autoimmune hepatitis, the number of demyelinating lesions was lower, in comparison with the previous image.
There is evidence to support the hypothesis of MS having an autoimmune inflammatory origin, defined by a genetic predisposition and basic immunological mechanisms, together with environmental factors. Several autoimmune inflammatory etiologies may affect the central nervous system similarly, such as Sjogren’s syndrome and primary biliary cirrhosis, autoimmune hepatitis (AIH), as MS, has no known etiology, so they both can be the expression of a heterogeneous syndrome with different clinical presentations and progression rates. Response to treatment with steroids, as well as the decrease in the number of demyelinating lesions seen on MRI control, supports the hypothesis of an autoimmune inflammatory origin, with common pathophysiological mechanisms to both diseases, which benefits from treatment with anti-inflammatory and immunosuppressive drugs.

### Bibliography


### Table 1. Clinical Cases Published: Association of Autoimmune Hepatitis and Multiple Sclerosis (2002-2008)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Gender</th>
<th>Age</th>
<th>AST/ ALT</th>
<th>Other Antibodies</th>
<th>AP?</th>
<th>AIH-MS</th>
<th>Biopsy Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1]</td>
<td>F</td>
<td>18</td>
<td>628/1116</td>
<td>IgA 437, IgG 1134, IgM 146, γ-GT 63</td>
<td>MS</td>
<td>ASMA (1/20)</td>
<td>Acute hepatitis</td>
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<tr>
<td>[12]</td>
<td>F</td>
<td>56</td>
<td>12x N</td>
<td>IgG ↑ γ-GT ↑×4 N</td>
<td>ANA (1/1280)</td>
<td>MS</td>
<td>Hyperthyroidism</td>
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<td>[12]</td>
<td>M</td>
<td>43</td>
<td>15x N</td>
<td>γ-GT ↑×8 N</td>
<td>ANA (1/2560)</td>
<td>MS</td>
<td>DM (IT)</td>
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<tr>
<td>[13]</td>
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<td>25</td>
<td>593/1146</td>
<td>γ-GT 142</td>
<td>-</td>
<td>MS</td>
<td>Necrosis; infiltrate (lymphocytes, eosinophils, and plasma cells); fibrosis</td>
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<tr>
<td>[13]</td>
<td>F</td>
<td>28</td>
<td>875/748</td>
<td>IgM↑, IgA↑</td>
<td>ANA (1/80)</td>
<td>MS</td>
<td>Centrilobular necrosis; mononuclear cell infiltration</td>
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<tr>
<td>[8]</td>
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<td>43</td>
<td>566/875</td>
<td>γ-GT 12 IU/L IgG 1785</td>
<td>ANA (1/80)</td>
<td>MS</td>
<td>γ-GT 124</td>
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<tr>
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<td>46</td>
<td>579/579</td>
<td>γ-GT 124</td>
<td>-</td>
<td>MS</td>
<td>Chronic active hepatitis; perportal inflammation; infiltrate (neutrophils and eosinophils)</td>
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<td>[14]</td>
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<td>19</td>
<td>1151/1317</td>
<td>IgG ↑</td>
<td>ASMA +</td>
<td>MS</td>
<td>Celiac disease</td>
</tr>
</tbody>
</table>

AST aspartate aminotransferase, ALT alanine aminotransferase, F female, M male, DAIH-MS interval between autoimmune hepatitis and multiple sclerosis onset, ANA antinuclear antibody, IgG immunoglobulin G, ASMA smooth muscle antibody, γ-GT gammaglutamyltranspeptidase, MS multiple sclerosis, ITDM insulin treated Diabetes mellitus, BD baseline diagnosis.

Table 1. Clinical Cases Published: Association of Autoimmune Hepatitis and Multiple Sclerosis (2002-2008)