Association of autoimmune hepatitis and multiple sclerosis: a coincidence?

Associação de hepatite autoimune e esclerose múltipla: coincidência?

Marta Sofia Mendes Oliveira, Joana Pires, Rosa Jorge Saudade

Internal Medicine Service. Infante D. Pedro Hospital – Baixo Vouga Hospital Center. Portugal

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.

Resumo

Hepatite auto-imune é uma inflamação crónica do fígado resultante da desregulação dos mecanismos de tolerância imunológica. A esclerose múltipla é também uma doença inflamatória, em que as células nervosas do cérebro e da medula espinal são danificadas. Apresenta-se o caso de uma mulher de 18 anos com esclerose múltipla, tratada com acetato de glatiramer e com interferão beta 1a. Sete meses após o início do tratamento, verificou-se alteração das enzimas hepáticas, com predomínio de citólise. Os achados clínicos e laboratoriais eram sugestivos de hepatite medicamentosa, o que levou à interrupção do tratamento com interferão, com melhoria do quadro. Um ano mais tarde, sem administrar interferão, surge novo episódio de citólise hepática. Foi submetida a biópsia do fígado, que revelou alterações da estrutura hepática causadas por um processo inflamatório, com degeneração extensa peri-venular de características inespecíficas. A análise de autoanticorpos foi positiva para os anticorpos anti-músculo liso.

Efetuado o diagnóstico de hepatite auto-imune, a doente iniciou tratamento com prednisolona e azatioprina, com boa resposta clínica e analítica. Além disso, documentou-se que as lesões desmielinizantes de esclerose múltipla se tornaram menores. Existem apenas alguns casos publicados que descrevem a associação de hepatite auto-imune com a esclerose múltipla. Discute-se a possibilidade de ambas as doenças terem a mesma origem inflamatória auto-imune.

Palavras-chave: Fígado; inflamatório; interferão; corticoesteróides

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[1]. 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[2]. It has an incidence of 1-2 / 100,000 inhabitants, and women are more affected than men, at a ratio of 3.6: 1[3]. 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[4]. 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%[5]. The established treatment is prednisolone in monotherapy or in combination with azathioprine; these immunosuppressive regimens promote a clinical, analytical and histological improvement[5].

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)[6]. 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)[6].

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

Correspondencia: martasoliv@gmail.com

Como citar este artículo: *Mendes Oliveira MS, Pires J, Jorge Saudade R*
Association of autoimmune hepatitis and multiple sclerosis: a coincidence?. Galicia Clin 2015; 76 (3): 124-126

Recibido: 04/04/2015; Aceptado: 30/06/2015

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

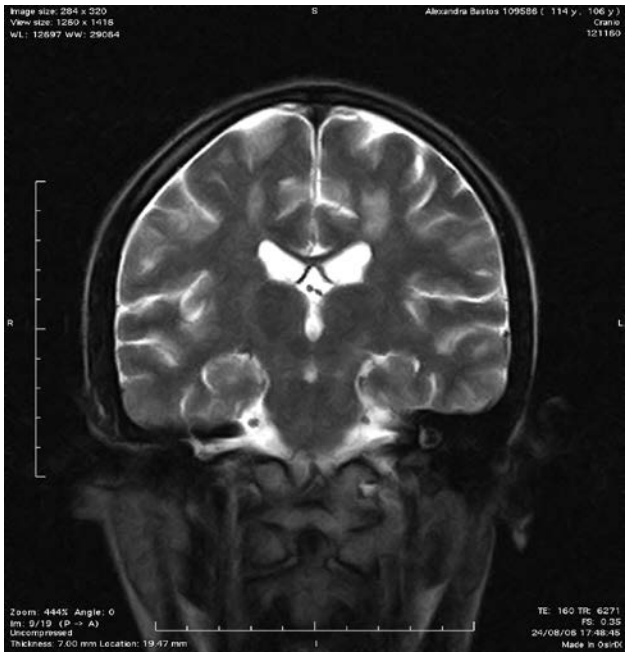
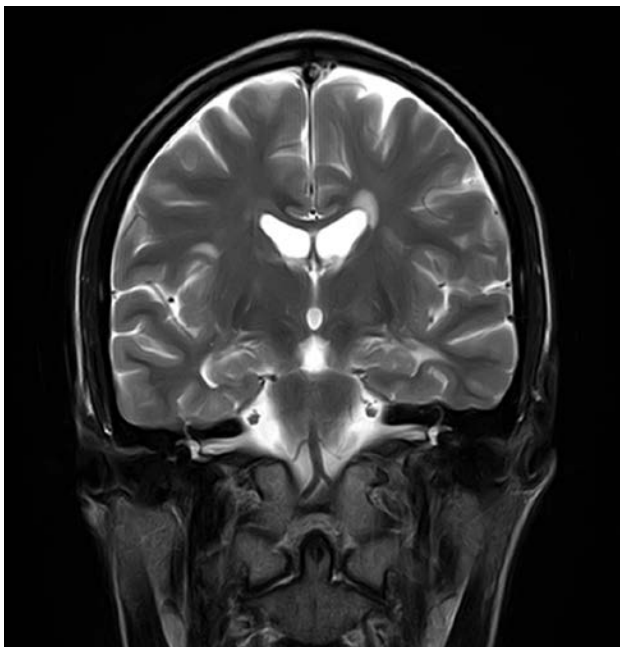


Figure 2. Magnetic Ressonance Imaging 2012 – after the treatment of the autoimmune hepatitis, the number of demyelinating lesions was lower, in comparison with the previous image.



therapy with prednisolone (20 mg) and azathioprine (50 mg). There was good clinical and analytical response during follow-up, with no complications; in late 2008 treatment was stopped. A magnetic resonance imaging was made in 2006 (figure 1), showing several demyelinating lesions of different types; however, compared to the magnetic resonance performed in 2012, the number of lesions decreased (figure 2). In 2013, at 26, the patient was treated with glatiramer acetate, remaining stable and with analytical values of liver function values within the normal range ever since.

Discussion

The persistence of episodes of acute recurrent hepatitis after the discontinuation of treatment with interferon raised the suspicion of a non-iatrogenic etiology. The application of the score above mentioned (Table 1) added a total of 15, sufficient to establish a definite diagnosis, confirmed by a value of 17 after treatment since there was complete response, even though we have to consider that as much as 22.5% of patients with MS show have circulating Antinuclear Antibodies (ANA)[7]. Although there may be adverse effects relating to interferon toxicity, it is unclear whether the first hepatic changes that the patient presented were an overlap of drug-induced disease and/or the onset of an autoimmune reaction.

MS is a demyelinating disease of the central nervous system and associated hepatic dysfunction is not always caused by the disease itself, but may result from several factors, such as drug toxicity, fatty infiltration and viral infection. Liver disease in patients with MS is in most cases caused by drugs. IFN-_, which increases the serum ALT level as a secondary effect, is one of the drugs known to cause liver damage in patients with MS[8]. Among drugs used to treat MS there are the ones which modulate T-cell activity and functions (i.e. interferons, anti-TNF and natalizumab) and could induce liver injury and possibly a heightened sensibility against self-antigens, induced by a immunomodulatory dysregulation (Th1 vs. Th2 and Th17), a spontaneous formation of autoantibodies (ANA, anti-dsDNS) and a direct imbalance of liver cytokines[7].

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[8]. 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[9]. 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[8], only a few cases have been described[11]. In Table 1 are summarized some of these registers, the first of which being the case under discussion.

The association of AIH, MS and celiac disease is an uncommon association, which probably occurs in an individual with a propensity to develop diseases mediated by Th1 cells[13]. Although both conditions occur on a specific population (young adults predominantly female), its prevalence may be underestimated since the AIH can be asymptomatic.

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

[Reference]	Gender	Age	AST/ ALT	Other	Antibodies	AP?	Δ AIH-MS	Biopsy Findings
[1]	F	18	628/1116	IgA 437, IgG 1134, IgM 146, γ-GT 63	ASMA (1/20)	MS		Acute hepatitis
[12]	F	56	↑2x N	IgG ↑ γ-GT ↑4x N	ANA (1/1280)	MS Hyperthyroidism		Portal lymphocytic inflammatory infiltrate
[12]	M	43	↑5x N	γ-GT ↑8x N	ANA (1/2560)	MS DM (IT)		Cirrhosis; portal and lobular inflammatory infiltrate (lymphocytic)
[13]	F	25	593/1146	γ-GT 142	-	MS		Necrosis; infiltrate (lymphocytes, eosinophils, and plasma cells); fibrosis
[13]	F	28	875/748	IgM↑, IgA↑	ANA (1/80)	MS		Centrilobular necrosis; mononuclear cell infiltration
[8]	F	43	566/875	γ-GT 12 IU/L IgG 1785	ANA (1/80) ASMA +	MS		Perivenular necrosis; interface heptitis
[13]	F	46	579/579	γ-GT 124	-	MS		Chronic active hepatitis; periportal inflammation; infiltrate (neutrophils and eosinophils)
[14]	F	19	1151/1317	IgG ↑	ASMA +	MS Celiac disease		Acute hepatitis

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, g-GT gammaglutamyltranspeptidase, MS multiple sclerosis, ITDM insulin treated Diabetes mellitus, BD baseline diagnosis.

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[14]. 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.

Conclusion

Through the study of this case, as well as through the analysis of other published reports, we should consider AIH in the differential diagnosis of patients with MS who have alterations in liver analytical parameters. Autoantibody screening should be done before starting biological therapies. Histological analyses of liver tissue are necessary to establish the diagnosis in suspected cases, even in patients in whom serum antibodies are negative. Special attention should be paid to the development of AIH after therapy with methylprednisolone or after IFN-_ and immunomodulatory drugs in MS patients in order to initiate immediate treatment with corticosteroids and azathioprine. AIH should also be considered and caution should be taken when re-exposing MS patients with previous hepatic damage to immunomodulatory drugs. Larger cohorts should help to determine whether the prognosis of patients with both MS and AIH differs from that of patients with only MS or AIH.

Abbreviations: Autoimmune hepatitis (AIH); Multiple Sclerosis (MS); interferon (IFN); aspartate aminotransferase (AST); Alanine transaminase (ALT); gamma-glutamyl transferase (GGT); Smooth Muscle Antibodies (SMA); antinuclear antibody (ANA); Anti-tumour Necrosis Factor (anti-TNF); Interleukin (IL).
There weren't any financial supports for writing this paper.

Bibliography

1. Vergani D CK, Bogdanos DP, Mieli-Vergani G.. Pathogenesis of autoimmune hepatitis. Clin Liver Dis 2002;6:727-37.
2. AJ. C. Autoimmune hepatitis. Part A: pathogenesis. Expert Rev. Gastroenterol Hepatol 2007;1:113-28.
3. Al-Chalabi T UJ, Portmann BC, McFarlane IG, Heneghan MA. Impact of gender on the long-term outcome and survival of patients with autoimmune hepatitis. J Hepatol 2008;48:140-7.
4. Feld JJ DH, Arenovich T, Marcus VA, Wanless IR, Heathcote EJ. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. HEPATOLOGY 2005;42:53-62.
5. Michael P. Manns AJC, James D. Gorham, Edward L. Krawitt, Giorgina Mieli-Vergani, Diego Vergani, and John M. Vierling. AASLD Practice Guidelines - Diagnosis and Management of Autoimmune Hepatitis. Hepatology 2010;51, No 6.
6. Gary M. Owens M. Managed Care Aspects of Managing Multiple Sclerosis. Am J Manag Care 2013;19 (16):307-12.
7. Lisotti AA, F; Brillanti, S; Mazzella, G. Severe acute autoimmune hepatitis after natalizumab treatment. Digestive and Liver Disease 2011;44:356-8.
8. Takahashi Aea. Development of autoimmune hepatitis type 1 after pulsed methylprednisolone therapy for multiple sclerosis:a case report World Journal of Gastroenterology 2008;14:5474-7.
9. Helmut Newmann AC, Michael Sailer, Peter Malfertheiner. Glatiramer acetate induced acute exacerbation of autoimmune hepatitis in a patient with multiple sclerosis. J Neurol 2007;254:816-7.
10. Vera von Kalckreuth AL, Christoph Schramm. Unmasking Autoimmune Hepatitis Under Immunomodulatory Treatmant of Multiple Sclerosis - not only Beta Interferon. American Journal of Gastroenterology 2008;10.1111:2143-66.
11. J de Seze VC-D, I Fajardy, S Delalande. Autoimmune hepatitis and multiple sclerosis: a coincidential association? Multiple Sclerosis 2005;11:691-3.
12. Corrieri-Baizeau C BI, Cottin V, Vukusic S. Hépatite auto-immune associée à une sclérose en plaques. Gastroentérologie Clinique et Biologique 2004;28:1186.
13. Ferrò M FD, Riccardi T, Adda E, Mainardi E. A case of multiple sclerosis with atypical onset associated with autoimmune hepatitis and silent coeliac disease. Neurol Sci 2008;29:29-31.
14. Nunez O ea. Hepatitia autoinmune en pacientes con diagnóstico de esclerosis múltiple. Gasterologia Hepatologia 2004;27 (9):521-4.