

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: <http://www.elsevier.com/locate/pjnns>

Case report

Acute liver failure and liver transplantation in a patient with multiple sclerosis treated with interferon beta

Dorota Kozielowicz^{a,*}, Małgorzata Pawłowska^b^aDepartment of Infectious Diseases and Hepatology, Faculty of Medicine, Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland^bDepartment of Children Infectious Diseases and Hepatology, Faculty of Medicine, Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland

ARTICLE INFO

Article history:

Received 28 March 2015

Received in revised form

24 August 2015

Accepted 28 August 2015

Available online 9 September 2015

Keywords:

Acute liver failure

Drug induced liver injury

Interferon β

Multiple sclerosis

ABSTRACT

In the treatment of multiple sclerosis (MS), interferon beta (IFN β) applies. It rarely can lead to acute liver failure (ALF).

A 42-year-old female with MS was admitted to the Department because of jaundice, general weakness, drowsiness and nausea. Four weeks earlier, she had started therapy with IFN β -1a. Liver tests made prior to initiation of IFN β -1a were normal but on admission to the Department exceed several times the upper limit. ALF was recognized and IFN β -1a was immediately stopped. In the fourth day of hospitalization, symptoms of hepatic encephalopathy have progressed. The patient was transferred to the Department of Transplantation, where hepatic coma developed and three days later the orthotopic liver transplantation was performed. In histopathological picture of the removed liver extensive necrosis and fibrosis dominated. Immunosuppressive therapy consisted of tacrolimus, mycophenolate mofetil and tapering prednisone. Within five years after surgery, there was no recurrence of symptoms of MS and the transplanted organ is functioning properly.

ALF is a rare complication of IFN β therapy but it can occur. The appearance of symptoms suggestive of liver injury should prompt extension of diagnosis and, if necessary, discontinuation of therapy.

© 2015 Polish Neurological Society. Published by Elsevier Sp. z o.o. All rights reserved.

1. Introduction

In the treatment of relapsing remitting multiple sclerosis (MS), interferon beta (IFN β)-1a or 1b apply. It has been shown to

delay the progression and reduce the frequency of relapses at least by 30%. Therapy with IFN β is associated with numerous side effects, among which the most common are, also known to treatment with interferon alpha of chronically infected HCV patients, local reactions, flu-like syndrome, hematological and

* Corresponding author at: Department of Infectious Diseases and Hepatology, Faculty of Medicine, Nicolaus Copernicus University in Toruń, ul. Św. Floriania 12, 85-030 Bydgoszcz, Poland. Tel.: +48 52 325 56 05; fax: +48 52 345 71 95.

E-mail address: d.kozielowicz@wsoz.pl (D. Kozielowicz).

<http://dx.doi.org/10.1016/j.pjnns.2015.08.006>

0028-3843/© 2015 Polish Neurological Society. Published by Elsevier Sp. z o.o. All rights reserved.

psychiatric disorders. Clinical studies and post-marketing observations have also identified the potential hepatotoxicity. Approximately in 23% and 67% of patients treated respectively with IFN β -1a at a dose of 30 mg intramuscularly (im) once a week or at a dose of 44 μ g subcutaneously three times weekly, an increase in the activity of liver enzymes was observed; mostly of mild and transient character [1]. However, IFN β can lead to acute liver failure. The paper presents the history of a patient requiring liver transplantation due to this reason.

2. Case report

A 42-year-old, Caucasian woman was admitted to the Department on June 16th 2010 because of jaundice, general weakness, drowsiness, nausea and vomiting. Four weeks earlier, she had started therapy with interferon β -1a (Avonex[®]

Biogen Idec Limited, Berkshire, United Kingdom) at a dose of 30 μ g im once a week, because of multiple sclerosis. She was diagnosed with clinical isolated syndrome (CIS) in December 2008 because of the incident of amblyopia quadrant of the left eye. At that time, magnetic resonance imaging of the brain (MRI) was made and did not show any lesions. She was treated with methylprednisolone at a dose of 1.0 g intravenously (iv) for three days with a full improvement. The second time the symptoms of retrobulbar optic neuritis with the accompanying general weakness appeared in April 2010. Again methylprednisolone was applied and then prednisone in decreasing doses, with a partial recovery. Brain MRI revealed demyelinating lesions in the occiput horn of the left lateral cerebral ventricle 17 mm \times 12 mm, numerous lesions disseminated in space and thickening of the optic nerve in intracanal section (Fig. 1). MS was diagnosed according to the Mc Donald criteria revised by Polman et al. [2]. The patient was qualified to

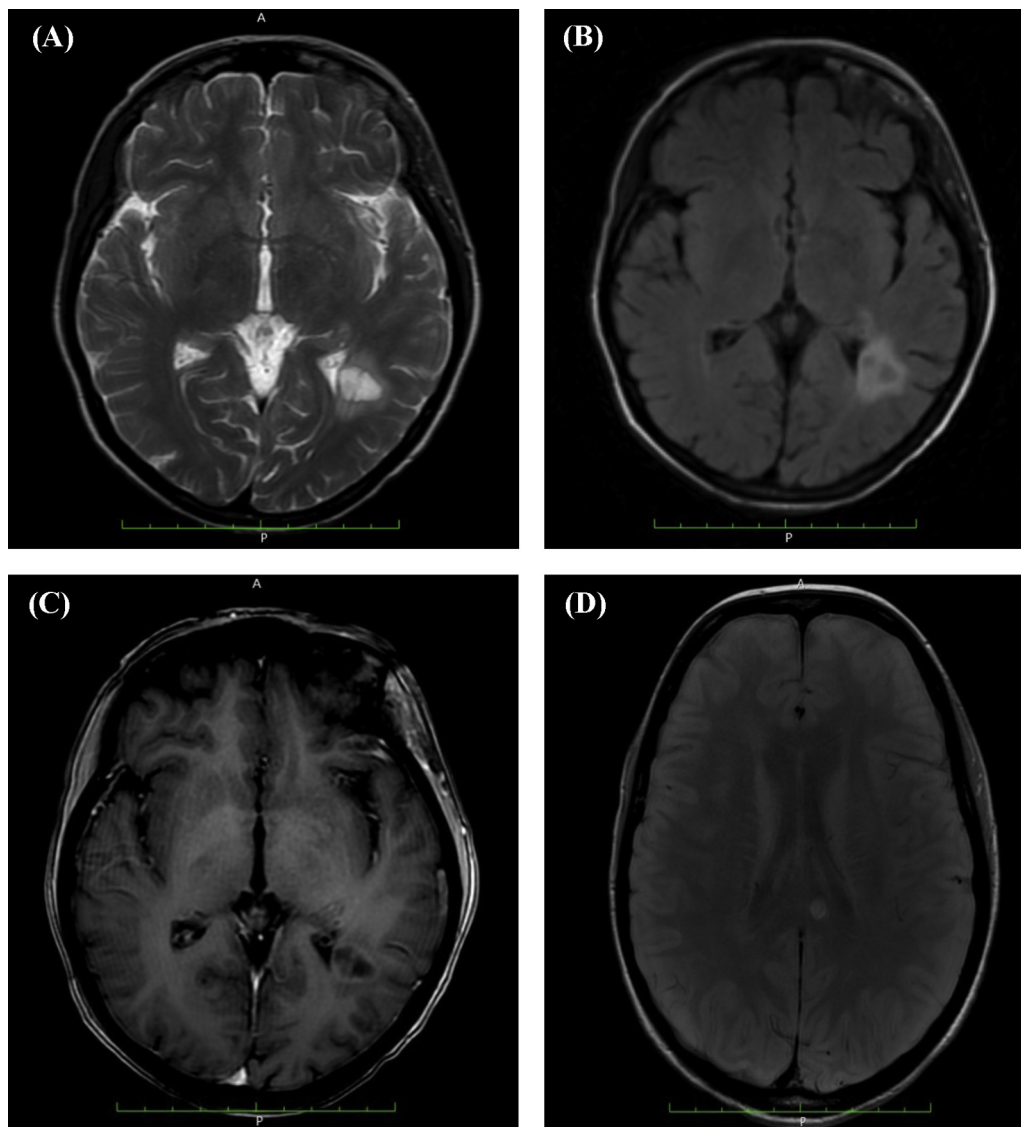


Fig. 1 – Brain MRI performed in April 2010 (before immunosuppressive therapy). Lesion of increased signal with edema in the occiput horn of the left lateral cerebral ventricle: (A) axial T2-weighted image; (B) axial FLAIR image; (C) axial, T1-weighted image after iv contrast; (D) lesion of increased signal in the corpus callosum, axial PD image.

IFN β -1a treatment, which began on May 18th 2010. Furthermore, her medical history has shown that she applied oral contraceptives for over 10 years and for three sumatriptan 1-2 times a month due to migraine. She did not consume alcohol, mushrooms, herbs, dietary supplements and did not take any other drugs. She denied any liver disease. Liver tests made immediately prior to initiation of interferon β -1a were within normal limits: alanine aminotransferase activity was 29 U/L (normal range < 33), aspartate aminotransferase 34 U/L (normal range < 34), γ -glutamyltransferase 19 U/L (normal range 5-36), bilirubin 8.55 μ mol/L (normal range < 17.1). On admission to the Department the values of liver tests exceed several times the upper limit (Table 1). Acute liver failure was recognized. The administration of interferon β -1a was immediately stopped and treatment with methylprednisolone (1.0 g iv daily), ornithini aspartas (15 g iv/day), rifaximin (1.2 g orally/day), supplementation of vitamin K (10 mg iv/day) and prophylactic antibiotics administration (ceftriaxone 1.0 g iv/day) was initiated. Viral hepatitis A, B and C, infections with cytomegalovirus, Epstein-Barr virus, herpes simplex virus, Wilson's disease and alpha-1 antitrypsin deficiency were excluded. High levels of antibodies were found against double-stranded DNA 42.5 IU/mL (normal < 10), U1 ribonucleoprotein 14.6 U/mL (normal < 5), cytoplasmic reacting with myeloperoxidase 20.8 U/mL (normal < 7) and Symphony 1.2 U/mL (normal < 0.7) (screening test for the detection of antinuclear antibody associated with systemic lupus erythematosus and other connective tissue diseases). Levels of immunoglobulins IgG, IgM, and IgA were within normal limits. Ultrasonography of the abdomen showed increased echogenicity and irregular echostructure of the liver and

a mild ascites. Magnetic resonance imaging revealed diffuse hepatic signal abnormality suggestive of acute inflammatory hepatic changes. The gastroscopy revealed no features of portal hypertension. In the fourth day of hospitalization, despite treatment symptoms of hepatic encephalopathy II \rightarrow III $^\circ$ have progressed. The patient was transferred to the Department of Transplantation, where hepatic coma developed and three days later the orthotopic liver transplantation was performed. The removed liver was very small: 15.5 cm \times 13 cm \times 7 cm. The histopathological findings of the removed liver revealed extensive fields of fresh necrosis and areas of postnecrotic fibrosis. Focally the liver tissue showed areas of massive necrosis and fibrosis and in the remaining areas one can observe portal-portal and portal-central bridging hepatic necrosis. Diffuse hepatic fibrosis caused replacement of normal liver lobular architecture by parenchymal nodules. Our attention was drawn by a prominent loss of interlobular ductules (ductopenia) in numerous portal areas. There were also moderate mononuclear cells inflammatory infiltrates within portal tracts, features of ductular reaction with increased number of ductular profiles within the areas of fibrosis and prominent bile stasis. All of those above described histopathological findings may correspond to extensive, drug induced hepatic injury. The postoperative complications were not observed. The patient in good general condition was discharged from hospital two weeks after liver transplantation. Immunosuppressive therapy consisted of tacrolimus (Prograf[®] Astellas Pharma, Berkshire, Ireland), mycophenolate mofetil (CellCept[®] Roche Pharma, Grenzach Wyhlen, Germany) and tapering prednisone. Within five years after surgery, there was no recurrence

Table 1 – Results of selected laboratory tests from the patient's treatment period.

Result/normal range	One day before admission to the hospital (15.06.2010)	1st day of hospitalization (16.06.2010)	2nd day of hospitalization (17.06.2010)	3rd day of hospitalization (18.06.2010)	4th day of hospitalization (19.06.2010)	One week after OLT
Hb (120-160 g/L)	134	119	116	126	128	110
WBC (4-10 \times 10 ⁹ /L)	6.24	9.1	8.3	21.7	18.9	8.5
Platelets (140-440 \times 10 ⁹ /L)	222	184	178	211	204	764
ALT (<31 U/L)	1045	830	634	575	471	36
AST (<31 U/L)	867	949	545	399	191	27
B. total/dir (<17.1/<3.42 μ mol/L)	301/174	282/213.6	286.4	319.4	-	20.7
ALP (35-104 U/L)	137	-	110	-	-	100
GGT (5-36 U/L)	266	-	165	-	-	103
INR (0.81-1.1)	2.37	2.38	2.38	2.15	1.73	0.96
Fibrinogen (1.8-3.5 g/L)	-	1.30	-	1.59	-	3.44
PT (9.4-13.5 s)	-	24.4	-	22.6	20.3	11.2
AT III (70-130%)	-	18.7	-	-	-	-
TP (64-83 g/L)	51.83	-	49.6	-	-	67
Al (40.2-47.6 g/L)	-	-	27.8	-	-	39
Cholesterol (<5.17 mmol/L)	4.24	-	3.0	-	-	-
Ammonia (31-123 μ g/dL)	-	98	-	108	-	-
Creatinine (44-80 μ mol/L)	80	36.24	30.05	22.98	32.7	53.9
Urea (2.1-7.1 mmol/L)	2.68	2.1	-	3.45	4.35	7.14
Glucose fasting (3.8-5.8 mmol/L)	-	6.55	11.54	6.99	7.04	4.27

Hb, hemoglobin; WBC, white blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; B. total/dir, total/direct bilirubin; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; INR, international normalized ratio; PT, prothrombin time; AT III, antithrombin III; TP, total protein; Al, albumin; OLT, orthotopic liver transplantation.

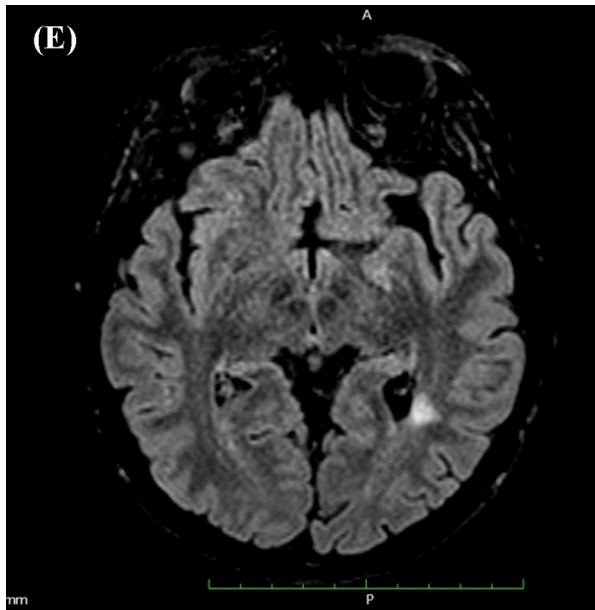


Fig. 2 – Brain MRI performed in October 2012 (after immunosuppressive therapy). (E) Partial remission of lesion showed on Fig. 1A–C, axial FLAIR image.

of symptoms of multiple sclerosis (Fig. 2) and the transplanted organ is functioning properly.

3. Discussion

Acute liver failure (ALF) is a dramatic but rare clinical syndrome marked by a sudden loss of hepatic function in previously normal individuals. It usually presents with coagulopathy and any degree of hepatic encephalopathy, the length of illness being considered anything ≤ 26 weeks. Currently in developed countries, the most common cause is acetaminophen overdose and idiosyncratic drug reaction [3]. The mechanism of IFN beta induced hepatotoxicity in MS patients is unknown. IFN β can probably cause liver injury as a result of an idiosyncratic reaction, a hypersensitivity reaction or it may indeed induce autoimmune reaction in an already susceptible host [4–6]. It is likely that the liver injury in our patient was due to an idiosyncratic reaction because it typically occurs within weeks of initial exposure to IFN β and may continue to evolve even after drug withdrawal. Short duration and low cumulative dose of IFN β (120 μ g) taken by the patient by the time of ALF and increase of symptoms despite discontinuation of treatment may confirm this hypothesis. In addition, lack of response to steroids and liver histology support the direct nature of drug induced liver injury. Although numerous autoantibodies were detected in the patient, involvement of the autoimmune mechanism in the development of acute liver failure is doubtful, because in approximately 45% of patients with MS, presence of autoantibodies is concluded before the start of treatment with interferon beta, mainly antinuclear and anti-smooth muscle antibodies, whose titer at the time of treatment fluctuates. It

has been proved that their mere presence and variable name during treatment with interferon beta does not justify a diagnosis of autoimmune diseases [7]. However, reports of the development of the autoimmune ALF after application of interferon beta were described [5,6].

In the patient's laboratory studies dominated hyperbilirubinemia and high activity of aminotransferases, reflecting mainly the damaged hepatocytes. The patient ingested for a long time oral contraceptives and sumatriptan but their share in the development of ALF seems unlikely. Contraceptives cause mainly the increase of cholestasis parameters whereas sumatriptan rarely causes small changes in aminotransferases.

Most of the IFN β induced liver damage cases are revealed during the first six, at the latest twelve months of use, so it is recommended to determine the level of bilirubin and aminotransferase levels every month during the first three months of treatment and then every three months, and always in the case of the onset of symptoms suggestive of liver injury [8,9]. This procedure allows to detect early damage to the dose-dependent IFN β . However, it does not matter in the prevention of idiosyncratic liver damages because, as in the present case, they are virtually impossible to predict. Some risk factors, linked to liver damage caused by IFN β and expressed in elevated liver test results, are known: male sex, high-frequency dose, first 6–15 months of treatment [1,9–11]. Female sex is risk factor for acute liver failure [10].

The patient within 5 years after liver transplantation showed no neurological symptoms indicating both the progress of MS and side effects of immunosuppressive drugs. It may emphasize beneficial effect of immunosuppressive therapy on the course of MS. It can be explained by the observation made in animal model. Tacrolimus used in mice markedly protects against demyelination and axonal loss [12].

It is very important for both patient and doctor to maintain the remission as long as possible. Currently the guidelines for management of MS relapse in patients after liver transplantation are not available. The immunomodulatory drugs for multiple sclerosis are associated with a variety of adverse drug reactions, including liver and cardiac injury, infections [13]. Readministering of IFN β is strictly contraindicated. Also, the use of fingolimod (an antagonist of normal endogenous sphingosine-1-phosphate) is contraindicated due to the increased risk of opportunistic infections in patients receiving immunosuppressive drugs [13]. Likewise natalizumab (monoclonal antibody which prevents migration of lymphocytes across the blood brain barrier by blocking alpha-4-integrin adhesion molecules) may increase the risk of common or opportunistic infections. Significant liver injury due to natalizumab is possible but rare [14]. Thus, choice of the treatment method depends on the experience of the doctor, relation of risks to losses and co-existing diseases.

The differential diagnosis of multiple sclerosis usually includes diseases which cause more than one neurological symptom and extend in a chronic or recurrent way and in the course of which MRI hyperintense there are variations in the sequences T2/PD. For patients diagnosed with MS and abnormal liver function primarily autoimmune liver diseases (autoimmune hepatitis, primary biliary cirrhosis), drug-induced liver injury and Wilson's disease (WD) should be taken

into consideration. In the first case, the diagnosis of liver disease may be ultimately decided as the result of liver biopsy in the second one through physical examination. WD should be suspected in patients with neurological signs not typical for MS and behavioral problems. Copper metabolism test (serum ceruloplasmin level, copper serum concentration, 24-h urinary copper excretion) and genetic analysis of mutation in the allele of the *ATP7B* gene confirm the diagnosis of WD. Kayser-Fleischer rings are not always present. Co-existence of these diseases seems to be coincidental. However, there could be potential influence of one disease upon another [15,16].

4. Conclusion

Liver damages caused by interferon beta use, are mostly mild, asymptomatic and transient and monitoring the level of bilirubin and aminotransferase levels allows for their early detection. ALF is a very rare complication of IFN β therapy but can occur. The appearance of symptoms suggestive of liver injury should prompt extension of diagnosis and, if necessary, discontinuation of therapy.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES

- [1] Chan S, Kingwell E, Oger J, Yoshida E, Tremlett H. High-dose frequency beta-interferons increase the risk of liver test abnormalities in multiple sclerosis: a longitudinal study. *Mult Scler* 2011;17(3):361-7.
- [2] Polman CH, Reingold SC, Edan G, Filipp M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "Mc Donald Criteria". *Ann Neurol* 2005;58(6):840-6.
- [3] Khashab M, Tector AJ, Kwo PY. Epidemiology of acute liver failure. *Curr Gastroenterol Rep* 2007;9(1):66-73.
- [4] Yoshida EM, Rasmussen SL, Steinbrecher UP, Erb SR, Scudamore CH, Chung SW, et al. Fulminant liver failure during interferon beta treatment of multiple sclerosis. *Neurology* 2001;56(10):1416.
- [5] Montero JL, Cerezo A, Fraga E, Barrera P, López-Cillera P, Costan G, et al. Acute liver failure in a patient with multiple sclerosis treated with interferon-beta. *Mult Scler* 2007;13(6):820.
- [6] Pietrosi G, Mandala L, Vizzini GB, Gruttadauria S, Minervini MI, Burgio G, et al. Fulminant hepatic failure and autoimmune disorders in patient with multiple sclerosis on interferon beta 1a: a fatal combination? *Transpl Int* 2008;21(5):502-4.
- [7] Speciale L, Saresella M, Caputo D, Ruzzante S, Mancuso R, Calvo MG, et al. Serum auto antibodies presence in multiple sclerosis patients treated with beta-interferon 1a and 1b. *J Neurovirol* 2000;6(Suppl. 2):S57-61.
- [8] Fontana RJ, Hayashi P, Bonkovsky HL, Kleiner DE, Kochhar S, Gu J, et al. Presentation and outcomes with clinically apparent interferon beta hepatotoxicity. *Digest Dis Sci* 2013;58(6):1766-75.
- [9] Tremlett HL, Oger J. Hepatic injury, liver monitoring and the beta-interferons for multiple sclerosis. *J Neurol* 2004;251(1):1297-303.
- [10] Francis GS, Grumser Y, Alteri E, Micaleff A, O'Brien F, Alsop J, et al. Hepatic reactions during treatment of multiple sclerosis with interferon-beta-1a: incidence and clinical significance. *Drug Saf* 2003;26(11):815-27.
- [11] Tremlett HL, Yoshida EM, Oger J. Liver injury associated with the beta-interferons for MS: a comparison between the three products. *Neurology* 2004;62(4):628-31.
- [12] Gold BG, Voda J, Yu X, McKeon G, Bourdette DN. FK506 and a nonimmunosuppressant derivative reduce axonal and myelin damage in experimental autoimmune encephalomyelitis: neuroimmunophilin ligand-mediated neuroprotection in a model of multiple sclerosis. *J Neurosci Res* 2004;77(3):367-77.
- [13] Kowalec K, Carleton B, Tremlett HL. The potential role of pharmacogenomics in the prevention of serious adverse drug reactions in multiple sclerosis. *Mult Scler Relat Disord* 2013;2(3):183-92.
- [14] Cross AH, Naismith RT. Established and novel disease-modifying treatments in multiple sclerosis. *J Intern Med* 2014;275(4):350-63.
- [15] Gunther P, Baum P, Then Bergh F, Hermann W. Morbus Wilson and multiple sclerose. Eine Koinzidenz. *Der Nervenarzt* 2010;81(2):226-8.
- [16] Dzieżyc K, Litwin T, Członkowska A. Multiple sclerosis in two patients with coexisting Wilson's disease. *Mult Scler Relat Disord* 2014;3(3):387-90.