Chronic hepatitis B with type 1 diabetes mellitus and peripheral neuropathy development during peg-interferon alpha-2a therapy

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Abstract

Peg-interferon alpha is a molecule frequently used in the treatment of chronic hepatitis B, C, and D, with immunomodulatory and antiviral activity. It is also used in some cancer types. It has been widely claimed that interferon alpha triggers autoimmunity, with its broad adverse effect profile.

Here we present the case of a 49-year-old male patient with chronic hepatitis B diagnosis, who developed type 1 diabetes mellitus and peripheral neuropathy during the treatment with peg-interferon alfa-2a. Within four months of initiation of treatment with peg-interferon alfa-2a, the patient presented to our clinic with tiredness, myalgia, arthralgia, and blood glucose level of 166 mg/dL. Four months later, on November 2013, his fasting blood glucose level was 287 mg/dL. The patient complained of thirst, decreased balance and gait changes; he was admitted to the gastro-hepatology clinic for a thorough evaluation. Endocrinology consultation was requested and the patient was diagnosed with type 1 diabetes mellitus. Insulin therapy and diabetic diet was started, and blood glucose and HbA_{1C} levels were monitored regularly thereafter. The endocrinologist recommended the evaluation of nerve conduction. The results of this examination showed metabolically-induced axonal demyelinating sensitive neuropathy with subnormal evoked potential amplitude and conduction velocity of sural nerve. For patients who will receive treatment with interferon alpha, especially those individuals with chronic hepatitis, pancreatic autoantibodies should be checked; close monitoring of glucose levels, neurological signs and symptom, prior to and during the treatment, are also mandatory.

Keywords: chronic hepatitis B, diabetes mellitus, peg-interferon alpha-2a, peripheral neuropathy.

Introduction

Hepatitis B virus (HBV) is a public health problem worldwide with an estimated 240 million (1) to 360 million chronic carriers (2). The prevalence of HBV is more pronounced in developing world (3). In Albania, a developing country in Southeast Europe, the prevalence of hepatitis B during the period 2004-2006 was 9.5% (4). Chronic hepatitis B and C is now usually treated with interferon-alpha but its side effects are numerous (5). PEG-interferon alpha-2a has a prolonged half-life and requires less frequent administration compared to interferon alpha (6). PEG-interferon alpha-2a is superior in treating HBV or HCV although its side effects are similar to that of conventional interferon alpha-2a (6). Interferon-stimulated genes regulate various biologic effects, including inhibition of viral replication of infected cells, inhibition of cell proliferation, immunomodulation, and the like (7).

Common adverse effects of PEG-interferon alpha-2a include flu-like syndrome, haematological abnormalities (neutropenia, anaemia, thrombocytopenia), cardiovascular system symptoms, gastrointestinal symptoms (nausea, vomiting), exacerbation of hepatitis, type I diabetes mellitus, autoimmune diseases, lung dysfunction, depression and retinopathy. Interferon alpha is known to activate autoantibodies and lead to autoimmune diseases (8-10). Autoimmune diseases such as type 1 diabetes mellitus, thyroid diseases, psoriasis, hemolytic anemia, rheumatoid arthritis, thrombocytopenia, systemic lupus-like syndromes and sarcoidosis have been reported as well (8-10). Type 1 diabetes mellitus is characterized by insulin deficiency due to autoimmune destruction of pancreatic beta-cells (11). Interferon alpha may elevate the serum level of interleukin1, which is cytotoxic to pancreatic islet cells and could eventually lead to type 1 diabetes mellitus (12).

Here we present a case of a male patient with chronic hepatitis B diagnosis who developed concomitant type 1 diabetes mellitus during the treatment with PEG-interferon alfa-2a.

Case report

A 49-year-old male patient presented at Gastro-Hepatology service of the University Hospital Center "Mother Teresa" in Tirana with chronic hepatitis B diagnosis in April 2013. There was no abnormality in the patient's physical examination prior to the treatment except for chronic asthenia, arthralgia and myalgia. There was no history of alcohol consumption, too.

Laboratory results were as follows: red blood cell count (RBC): $5.65x10^6/mm^3$; haemoglobin 16.0 g/dL; white blood cell count: (WBC) 4,800/µl and platelet count 121,000/µl; fasting blood glucose: 102 mg/dL (Normal value: 70-105 mg/dL); urea: 32 mg/dL (N: 10-50 mg/dL); creatinine: 1.2 mg/dL (N: 0.6-1.4 mg/dL); ALT: 43 IU/L; AST: 32 IU/L; GGT 21U/L; alkaline phosphatase: 51 IU/L (N: 0-258 IU/L); total bilirubin 0.8 mg/dL (N: 0.1-1.2 mg/dL); total protein 7.4 g/dL (N: 6.0-8.3 g/dL); cholesterol 131 mg/dL (N: 140-220 mg/dL) and triglycerides 105 mg/dL (N: 50-150 mg/dL).

The patient was started a 180 mcg PEG interferon alpha-2a regimen once a week. During the follow-up, on July 2013, the fasting glucose level was 166 mg/dL. Four months later, on November 2013, his fast blood glucose level was measured at 287 mg/dL. The patient complained of thirst, decreased balance and changes of his regular gait. An endocrinology consultation was requested and the patient was diagnosed with type I diabetes mellitus. The treatment of the newly installed disease included insulin therapy and diabetic diet, as well as regular monitoring of blood glucose and HbA_{1C} levels. The endocrinologist recommended the evaluation of nerve conduction as well. The results of this examination showed metabolically induced axonal demyelinating sensitive neuropathy with abnormal evoked potential amplitude and nerve conduction velocity of nerve suralis.

Discussion

As mentioned previously, the literature suggests that interferon therapy may lead to autoimmune

diseases (8-10,13). PEG-interferon alpha-2a, despite being superior to conventional interferon alpha-2a, has the same side effect properties (6). Among 677 patients with chronic hepatitis C and being treated with interferon alpha, five of them or 0.7% developed type 1 diabetes mellitus (14), whereas other reports suggest the incidence of type 1 diabetes mellitus after interferon therapy at 0.09% to 0.7% (15,16). Conversely, the prevalence of pancreatic auto-antibodies seems to rise following the treatment with interferon alpha (17). The fact that interferon therapy might newly induce type 1 diabetes mellitus has been reported in many instances in the international literature, mainly through case reports (17-20). The development of type 1 diabetes mellitus following interferon alpha therapy for chronic hepatitis C was first reported in 1992 (18) and suggested that in predisposed individuals interferon alpha triggers diabetes. Therefore, patients should be tested for insulin antibodies before initiating interferon therapy (17). In other cases, the disease (chronic hepatitis C) was eradicated following interferon alpha therapy but diabetes was installed (19). Rarely, PEG-interferon alpha therapy could induce more than one autoimmune disorder simultaneously (20,21) such as the case of a female patient who developed both type 1 diabetes mellitus and hyperthyroidism (20). Usually, the development of type 1 diabetes mellitus due to interferon alpha therapy is permanent (17-21).

Apart from autoimmune disorders, interferon therapy could lead to psychiatric side effects (22,23) and suicidal thoughts (24) that are not to be neglected as they affect the quality of life of patients and may limit treatment (25). In a prospective randomized trial that examined the effectiveness of psychiatric counselling compared to clinical monitoring alone among 211 patients with chronic hepatitis C and receiving interferon (25). In total, 22 patients or 10.4% developed severe psychiatric symptoms but the prevalence was about four times higher in the group that did not receive psychiatric counselling prior to therapy (16.1% vs. 4.7%, respectively) (25). All patients that developed psychiatric disorders were obliged to interrupt interferon therapy (25) and were being treated with antidepressants (25). As the authors stated: "*if life-threatening hematologic side effects were well-tolerated and flu-like symptoms were manageable in all patients, psychiatric side effects were unpredictable and potentially dangerous. Psychiatric complications are among the most dangerous side effects and they range from anxiety, irritability, and depression to live-threatening psychosis and suicide*" (25). This example highlights the potential of interferon therapy to induce psychiatric symptoms which may force treatment to stop. Therefore, it is important to take into consideration the psychiatric aspects of interferon therapy and provide the necessary services in order to prevent them and ensure the continuation of treatment.

Conclusion

In conclusion, PEG-interferon alpha might trigger autoimmune disorders, including diabetes mellitus type 1 in patients with risk factors because of its complicated effects on immune system. Therefore, patients who are planning to be treated with peg-interferon should be evaluated for autoimmune parameters both prior to and during the treatment. On the other hand, patients on PEG-interferon therapy who develop high glucose levels and nonspecific neurological findings should be referred for a full neurological evaluation.

Conflicts of interest: None declared.

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