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Axonal neuropathy and hearing loss associated with alpha interferon treatment in chronic hepatitis B: A case report

Kronik hepatit B'de alfa interferon kullanımına bağlı gelişen aksonal nöropati ve işitme kaybı: Olgu sunumu

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The effect of interferon alpha in chronic viral hepatitis and common side effects are well known, but axonal polyneuropathy and hearing loss have been rarely reported. A 58-year-old woman was administered interferon alpha-2a (9 MU/3 times a week) and lamividin (100 mg daily) with the diagnosis of chronic hepatitis B. At the fifth month of the treatment gait disturbance and tinnitus developed. In her neurological examination tandem gait was ataxic on the right side. Cerebral magnetic resonance imaging performed to elucidate a probable cerebral pathology revealed nonspecific millimetric hyperintense lesions thought to be related with her hypertension anamnesis. Electroneuromyography demonstrated mild axonal polyneuropathy. The finding of pure-tone audiometry was sensorineural hearing loss in her left ear. Our diagnosis was axonal polyneuropathy and sensorineural type hearing loss as a side effect of interferon. In conclusion, the development of polyneuropathy and sensorineural hearing loss in the same patient may suggest autoimmunity as the cause of these side effects.

Key words: Axonal neuropathy, hearing loss, interferon

Kronik viral hepatitlerin tedavisinde etkinliği kanıtlanmış olup, yaygın olarak kullanılan Alfa interferona bağlı aksonal nöropati ve işitme kaybı ender rastlanan yan etkilerdendir. 58 yaşında bayan hasta, kronik hepatit B tanısı ile interferon alfa-2a; haftada 3 gün 9 MÜ ve lamividin lOOmg/gün başlandı. Tedavinin 5. ayında dengesizlik, kulak uğultusu şikayeti ile başvuran hastanın nörolojik muayenesi tandem yürüyüş sağa ataksik dışında normal idi. Serebral patolojiyi ekarte etmek için yapılan Beyin Mağnetik Resonans Görüntülemede; milimetrik nonspesifik hiperintens odaklar görüldü. Bu bulgu öyküdeki hipertansiyon ile uyumlu olarak düşünüldü. Elektronöromyogram bulguları hafif aksonal polinöropati ile uyumlu idi. Odyometride sol kulakta sensorinöral tip işitme kaybı mevcuttu. Hastada alfa interferona bağlı aksonal polinöropati ve sensorinöral işitme kaybı düşünüldü. Sonuçta, ayni hastada hem polinöropati, hem de sensorinöral işitme kaybının beraber olması etyolojide otoimmünitenin yer aldığını düşündürebilir.

Anahtar kelimeler: Aksonal nöropati, işitme kaybı, interferon

INTRODUCTION

Interferons (IFNs) are cytokines produced by lymphocytes and macrophages whose antiviral, antitumoral and immunomodulatory properties are increasingly exploited for therapeutic purposes. Interferon alpha (IFN-α) has been accepted for use in a wide range as therapy for hepatitis B virus (HBV) and hepatitis C virus (HCV) infections (1). Systemic side effects are common with IFN. In general, neurological side effects involve the central nervous system and develop after long-term and high-dose drug use. Peripheral nerve involvement and ototoxicity of IFN have been rarely reported (2-10).

In this case, we describe a patient in whom axonal polyneuropathy (PNP) and sensorineural (S/N) type hearing loss developed during treatment with IFN, which can be an indicator of an autoimmunity mechanism.

CASE REPORT

A 58-year-old female, who had been suffering from hepatitis B for 31 years, applied to the Gastroenterology Department for follow-up. She had hypertension (HT) and was using ramipril-hydrochlorothiazide, 2.5 mg daily. Her initial physical and neurological examinations were normal.

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Results of laboratory studies such as serum glucose, urea, creatinine, lipids, electrolytes, protein, creatinine phosphate (CPK), bilirubins, ferritin, thyroid stimulating hormone (TSH), blood cell count and cryoglobulin levels were all in normal limits. Also alkaline phosphatase (ALP), gammaglutamyl transaminase (GGT), and amylase were normal. Aspartate aminotransferase (AST) was 82 U/l (N: 1-37), alanine aminotransferase (ALT) was 133 U/l (N: 1-42) and erythrocyte sedimentation rate, at 32/hour, was high. HbsAg, Anti HBC total, and Anti Hbe were positive; HbeAg, Anti HCV, and Anti HDV were negative. HBV-DNA was positive. Liver biopsy results indicated Knodell's score: HAI: 11, Grade 2 chronic hepatitis B.

With the diagnosis of chronic hepatitis B, IFN α 2a (9 mu 3 times weekly) and lamividin (1 tablet/daily) were added to her treatment. After five months of therapy she noted gait ataxia, tinnitus at the left ear, paraesthesia and mild burning distally in both feet, and was referred to the neurology polyclinic. Her neurological examination was normal except for ataxic tandem gait on the right side. TSH was 2.70 uIU/ml (N: 0.4-4.0), vitamin B12: 280 pg/ml (N: 160-900) and Mate: 5.5 mg/ml (3-17), all in normal limits.

Cerebral magnetic resonance imaging (MRI) revealed nonspecific millimetric hyperintense lesions in the white matter near the right ventricular posterior horn and at the right frontal lobe. Bilateral carotid and vertebral Doppler ultrasonography were normal. We planned an electromyography (EMG) to clarify the etiology.

Electromyography was concordant with axonal PNP (right peroneal nerve distal latency was 6.60 msn, amplitude: 1.6 mV, velocity: 39 m/s; left peroneal motor distal latency was 6.0 msn, amplitude: 2.0 mV, velocity: 40 m/s. F latency was 50 msn at the right side and 45 msn at the left side). Needle examination of bilateral extensor digitorum brevis (EDB) muscles showed moderate chronic reinnervation. tSEP was normal.

Her pure tone audiometry demonstrated S/N type hearing loss (air/bone: 57/56; speech reception threshold (SRT): 60; speech discrimination (PB): 88; MCL: 100 dB; UCL: 12 dB).

The diagnosis of the patient was PNP and S/N type hearing loss at the left ear as a side effect of IFN. The treatment was stopped. At her two-month follow-up, she reported that her complaints such as paraesthesia, burning of lower extremities and dizziness had significantly improved. In her neurological examination after the fifth month, her complaints of tinnitus and gait ataxia on the right side were still present. Follow-up EMG was normal. Follow-up audiometry was unchanged.

DISCUSSION

In this case, the results of tests led to the diagnosis of PNP and S/N type hearing loss attributable to IFN side effects. We believe the existence of both of these rare side effects, especially in the same patient, suggests that the same mechanisms may be effective in the pathogenesis.

To evaluate the cerebral pathology, such as intracranial tumors or vasculitis, which could be the etiology of ataxia and tinnitus, a cerebral MRI was performed revealing millimetric nonspecific hyperintense lesions, which could have been related with her hypertension anamnesis.

Development of mild PNP has been observed in patients taking IFN-α for HBV infection. Although the pathomechanism underlying peripheral neuropathy associated with IFN is unknown, it must be kept in mind that these patients may have an underlying disease, such as HCV, cryoglobulinemia or hypothyroidism, that may itself cause peripheral nerve dysfunction (5,11). However, data in the literature are consistent with the possibility that IFN-α itself may cause peripheral neuropathy (12). In our case, the possibility of HCV, cryoglobulinemia or hypothyroidism was excluded. According to the hypothesis of La Civita et al. (13), an indirect effect of IFN-α due to its immunoregulatory and antiviral activity can be an explanation for the PNP. It has been reported that in in vivo and in vitro studies, IFNs amplify autoantibody production and may upregulate gene transcription of class I major histocompatibility complex (MHC) antigens. Despite the protective effects of the drug against induced autoimmunity, the administration of IFN-α may trigger autoimmune phenomena in immunologically predisposed patients, while suppressing autoimmunity in others. There are several reports of autoimmune disorders associated with IFN-α treatment including autoimmune thyroid disease and immune thrombocytopenia (14). Furthermore, IFNs may also have an inhibitory effect on DNA and RNA synthesis as well as protein metabolism. Interference with the biosynthetic process of neurons could induce dysfunction; however, no evidence to support this mechanism has been forthcoming (4).

Ototoxicity is a rare side effect of IFN. In a prospective study with 49 patients, auditory disability (tinnitus and/or hearing loss) was found in 43.8% of patients and S/N type hearing loss was found in 36.9% of patients. Most patients recovered 7-14 days after the discontinuation of IFN (7). In this study, rapid improvement of auditory function after discontinuation of IFN suggests microvascular pathogenesis. Thrombocytopenia induced by IFN might have caused a microvascular accident in the inner ear. Ototoxicity is reversible if the diagnosis is made early in the course (8). In our case auditory disability was not associated with thrombocytopenia. Cadoni et al. (9) detected anti-endothelial cell antibodies in a patient with sudden hearing loss. The finding of these antibodies suggests an association between sudden hearing loss and microvascular damage during IFN therapy. The relation between autoimmunity and hearing loss was also reported in other studies (7, 16, 17). We believe the autoimmune mechanism, which was discussed in polyneuropathy, might also be the etiologic factor behind the sudden hearing loss in our patient.

However, the drug itself may cause direct toxicity to the auditory nerve hairy cells (10).

The side effects of IFN are mostly reversible when the drug is stopped. But in our patient, despite the improvement in the clinical signs of PNP and the findings of the EMG at the fifth month, her hearing loss persisted. This could be from the cumulative effect of the drug.

In conclusion, we believe that in cases of development of PNP and S/N hearing loss in the same patient, autoimmunity may be the cause of these side effects.

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