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CASE REPORT

Bell's palsy and choreiform movements during peginterferon α and ribavirin therapy

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Abstract

Neuropsychiatric side effects of long-term recombinant interferon-α therapy consist of a large spectrum of symptoms. In the literature, cranial neuropathy, especially Bell's palsy, and movement disorders, have been reported much less often than other neurotoxic effects. We report a case of Bell's palsy in a patient with chronic hepatitis C during peginterferon-α and ribavirin therapy. The patient subsequently developed clinically inapparent facial nerve involvement on the contralateral side and showed an increase in choreic movements related to Huntington's disease during treatment.

Key words: Interferon α; Bell's palsy; Neurotoxicity; Huntington's disease

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INTRODUCTION

Neuropsychiatric side effects of long-term recombinant interferon-α (IFN-α) therapy consist of a large spectrum of symptoms. Organic personality syndrome, organic affective syndrome, psychotic manifestations, and seizures are more common side effects of IFN-α, whereas cranial neuropathy and movement disorders are less common[1].

We present a patient with chronic hepatitis C who showed an increase in choreiform movements associated with Huntington's disease (HD), and also developed Bell's palsy during treatment with pegylated interferon (peginterferon) and ribavirin.

CASE REPORT

A 54-year-old woman presented with anti-hepatitis C virus (HCV) positivity and elevated alanine aminotransferase (ALT) levels in February 2007. After documentation of PCR-based HCV viremia, she underwent liver biopsy. As pathological examination revealed stage Ⅲ fibrosis, it was planned to give her antiviral therapy that consisted of peginterferon-α and ribavirin. However, she had a history of minor choreiform limb movements for the past few years, but no cognitive impairment was observed. Her mother and sister had similar movements, and her mother had dementia consistent with HD. She also had been taken L-thyroxine for hypothyroidism for a few years. Although genetic analysis for exclusion of HD was proposed before starting antiviral therapy, the patient preferred to start therapy without genetic analysis for HD. She commenced peginterferon-α2b 100 μg once weekly and ribavirin 1000 mg/d in May 2007. In the third month of therapy, she had a 2 log decrease in HCV viral load.

After the fourteenth dose of peginterferon, she suffered pain behind her right ear, followed by dropping of the right side of the face. She attended the emergency

service of a local hospital, and she was started on anti-inflammatory therapy, but not on steroid therapy, because of the possibility of increasing HCV viral load. She then attended an outpatient clinic of the neurology department in our hospital. Neurological examination revealed right-sided Bell's palsy of House-Brackmann grade V[2]. The right facial nerve had 90% degeneration on electroneurography (ENG). No motor unit potentials were identified by needle electromyography (EMG). Contrast-enhanced magnetic resonance imaging (MRI) of the inner ear showed abnormal enhancement of the intracanalicular portion of the right facial nerve. Serological examination of some viral diseases revealed that herpes simplex virus (HSV) type Ⅰ IgG and anti-cytomegalovirus IgG were positive, whereas IgM tests for these viruses were negative. IgG and IgM tests for HSV type Ⅱ were also negative. She stopped antiviral therapy and was given anti-inflammatory therapy. An operation for facial nerve palsy was advised by the consultant in otorhinolaryngology, but hypothyroidism, most likely caused by inappropriate usage of oral thyroid hormone therapy, was found on preoperative screening tests. Two months after the facial symptoms began, she was euthyroid, and she underwent surgery for facial nerve decompression. She promptly experienced a virological and biochemical relapse after cessation of antiviral therapy. Three and a half months after facial paralysis, she chose to continue antiviral therapy, but this time peginterferon-α2a 180 μg was reinstated along with ribavirin. Two and a half months after the operation, facial movements were shown to be improved and graded as House-Brackman 3 on the right side. The right facial nerve had 48% degeneration upon ENG. We also observed reinnervation potentials on needle EMG. MRI of facial nerves performed after 5 mo of the second round of antiviral therapy revealed contrast enhancement of bilateral facial nerves, even though she had no clinical findings on the left side of her face. At the same time, the patient reported a noticeable increase in her choreiform movements, which were not found to be related to L-thyroxin overdose, after performing thyroid function tests. Upon neurological examination, clear choreiform movements of her upper and lower limbs were observed. There was no cognitive deterioration. Genetic analysis revealed increased CAG repeat length (23/43) consistent with HD. Her movement disorder did not deteriorate further and she did not experience facial palsy on the other side despite continuing therapy, but she was treated with systemic steroids during the last 2 wk of therapy to prevent overt facial palsy. She completed the 48-wk course of antiviral therapy. Although her choreic movements decreased upon completion of antiviral therapy, a prominent improvement in her movement disorder was observed with tetrabenazine (50 mg/d), which was started 3 mo after completion of antiviral therapy.

DISCUSSION

Bell's palsy is often idiopathic, but has been linked to some viral infections, particularly with herpes viruses[3,4]. Other infections, such as human immunodeficiency virus infection and Lyme disease, may also lead to idiopathic facial paralysis. Neither acute nor chronic HCV infection has been implicated previously in Bell's palsy, but IFN-α may have a role[5].

IFN-α, or peginterferon, together with ribavirin are the current treatment regimen for chronic hepatitis C. Large studies have shown that whereas flu-like symptoms and reversible hematological cytopenia are common side effects of this treatment regimen, more serious side effects are rare. In a large retrospective study from Italy, with a total of 11 241 patients who received IFN-α, new neurological problems including seizures and neuropathy occurred in less then 10 patients[6]. In a study of 677 Japanese patients treated with high-dose IFN, only one suffered a neurological complication, and developed sudden hearing loss[7]. However, psychiatric symptoms such as depression or anxiety have been seen commonly during IFN treatment. The reported frequency of neurotoxicity, including psychiatric side effects during IFN treatment ranges from 25% to 33%[8]. In another study from Italy, 108 out of 441 patients treated with IFN plus ribavirin for hepatitis C failed to finish combination therapy because of adverse effects. Ten patients suffered from neuropsychiatric problems: six presented with depression or anxiety, one with erectile dysfunction, one with seizures, one with vertigo and one with peripheral neuropathy[9]. There are also reports of IFN therapy leading to ischemic optic neuropathy, retinopathy, peripheral neuropathy, oculomotor neuropathy and trigeminal sensory neuropathy[1].

We found only six cases of Bell's palsy associated with IFN, in our literature search[5,10-12]. However, one case was associated with peginterferon-α[10]. Ogundipe *et al*[11] firstly documented two cases of Bell's palsy that developed during IFN-α and ribavirin therapy for chronic HCV. In both cases, facial palsy developed a number of months after commencing therapy and resolved, one with and one without cessation of therapy. The authors have suggested that a neuropathic effect of IFN-α2b on the facial nerve may result in facial paralysis. In another report including two patients with chronic HCV infection, Bell's palsy occurred during treatment with IFN-α2b and ribavirin at week 7 in one patient and week 12 in another[12]. Facial paralysis resolved in both cases after withdrawal of antiviral therapy. However, one of these patients experienced Bell's palsy shortly after an outbreak of HSV oral stomatitis. Thus, it is difficult to implicate exclusively combination therapy as the etiology for this case of Bell's palsy.

Hoare *et al*[5] have reported that three patients with chronic HCV infection also developed Bell's palsy during combination therapy, with spontaneous resolution after withdrawal of treatment. Two of the patients had immune-mediated baseline disease, ulcerative colitis and focal segmental glomerulonephropathy, which may have increased their risk of complications such as Bell's palsy.

The present case is, to the best of our knowledge, the second case of Bell's palsy associated with peginterferon

therapy reported in the literature. Bilateral facial nerve involvement is another interesting feature of our case. Hypothyroidism may be another cause for the primary right-sided palsy. However, subclinical involvement of the other facial nerve, which was found to be contrast-enhanced by MRI, during the second round of antiviral therapy, supported the suggestion of IFN-induced neurotoxicity.

Some adverse effects of IFN are thought to be caused by immune dysregulation, and a good example is autoimmune thyroiditis[13]. Previous studies on Bell's palsy have shown that it may be the result of an attack on cranial nerve Ⅶ by lymphocytes that sensitized to the Schwann cell membrane of the nerve itself[14]. Thus cell-mediated immunity, augmented by peginterferon and ribavirin, may target Schwann cells of cranial nerve Ⅶ and consequently lead to facial paralysis. Another possible mechanism might involve microvascular lesions that result from vasculitis or vasospasm, because there is evidence of IFN-α-induced retinal abnormalities, including ischemic lesions, cotton wool exudate, capillary occlusion or retinal hemorrhage[15,16].

To the best of our knowledge, four cases of chorea, associated with IFN-α were have been reported in the literature so far[17-20]. These were not associated with HD. Choreiform movements may increase during IFN-α therapy, since it affects dopaminergic pathways. Long-term IFN-α therapy acts as a dopamine antagonist by altering dopaminergic pathways through an opioid-receptor-associated action, and may cause choreic movements by dysfunction of basal ganglia-thalamocortical loops[17].

Bell's palsy and movement disorders are rare complications of IFN therapy. We suggest that the underlying mechanisms involve autoimmunity or neurotoxic effects of IFN on the neuroendocrine system and neurotransmitters, thus physicians should be aware of these rare neurotoxic side effects of IFN-α.

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