

Pegylated interferon/ribavirin-associated sudden hearing loss in a patient with chronic hepatitis C in Brazil

ABSTRACT

Sudden hearing loss is defined as a sensorineural hearing loss, equal to or greater than 30 dB, at three or more consecutive frequencies, which takes place within 72 hours. Both peginterferon and ribavirin are well-known to be associated with significant adverse effects, but sudden hearing loss is uncommon. We report a 65-year-old male patient who developed sudden-onset hearing loss during combination therapy with pegylated interferon-alpha and ribavirin for chronic hepatitis C. Peginterferon and ribavirin may cause sudden hearing loss that may not recover after discontinuation of therapy. Immediate treatment for all possible etiologies is essential, along with targeted investigations and early referral for an Ear, Nose and Throat specialist. Physicians should be aware of the possible ototoxic effects of peginterferon and ribavirin combination therapy requiring appropriate surveillance.

Keywords: hepatitis C; chronic; hearing loss; sudden; interferon-alpha.

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INTRODUCTION

Sudden hearing loss (SHL) is defined as a sensorineural hearing loss, equal to or greater than 30 dB, at three or more consecutive frequencies, which takes place within 72 hours.¹ Several suggested theories attempt to elucidate the etiopathogenesis of SHL, including autoimmune diseases, vascular insults, infectious diseases and ototoxic drugs.²⁻⁵ To our knowledge hepatitis C virus has not yet been associated with SHL. Pegylated interferon in combination with ribavirin is the treatment of choice for patients with chronic hepatitis C. Both peginterferon and ribavirin are well-known to be associated with significant adverse effects, but SHL is uncommon. We report a 65-year-old male patient who developed sudden-onset hearing loss during combination therapy with pegylated interferon-alpha and ribavirin for chronic hepatitis C.

CASE DESCRIPTION

A 65-year-old man with a history of chronic hepatitis C was referred to our department for further evaluation. He was 170 cm tall and weighed 74 kg. He reported to have systemic arterial hypertension and had been taking hydro-

chlorothiazide 25 mg and enalapril 40 mg daily for two years without any adverse effects. His initial physical and neurological examinations were normal. Serum levels of glucose, urea, creatinine, lipids, electrolytes, alkaline phosphatase, bilirubin, gammaglutamyl transferase, blood cell count, ferritin, were within normal limits. Alanine aminotransferase (ALT) was 62 UI/L (upper limit of normal < 45), aspartate aminotransferase (AST) was 39 UI/L (upper limit of normal < 45 UI/L). Antinuclear, anti-smooth muscle, anti-liver-kidney microsome 1 and anti-mitochondrial antibodies were negative. His viral load was 500,000 RNA IU/mL and the hepatitis C genotype was 1a. Liver biopsy revealed chronic hepatitis with moderate activity and stage II fibrosis (Metavir F2-A2). Combination therapy was started with PEG-IFN- α -2a subcutaneously (180 μ g per week) and ribavirin (1,000 mg/day). The patient responded well, his aminotransferase levels normalized, and HCV-RNA was undetectable at weeks 12 and 24. Twenty-eight weeks after initiation of therapy, he suddenly developed severe hearing loss in the right ear. He did not complain of any visual problems, dysphagia, dysarthria, sensory or motor deficits. He denied any recent flu-like symptoms or fever, chills,

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or night sweats. His physical examination at this time was otherwise unremarkable. Six days after the beginning of his symptoms (SHL on right ear) he was attended at the "Sudden Hearing Loss Section" of the Otolaryngology Department, *Hospital das Clínicas* of FMSUP, São Paulo. The initial audiometric test showed profound hearing loss on right ear. He had begun SHL treatment three days after the beginning of the first symptoms with dexamethasone 8 mg daily for 15 days, pentoxifylline 1,200 mg and vitamin A 50,000 IU daily for 30 days each, prescribed during first-aid clinic appointment. As the patient did not show any improvement with the usual SHL drug therapy, intratympanic steroids were proposed. Dexamethasone 2 mg was administered by instilling the steroid solution through the posteroinferior area of the tympanic membrane using a tuberculin syringe and a spinal needle, three times a week during two weeks; however, no audiometric improvement was observed. During routine SHL investigation blood exams revealed mild anemia with 10.6 g/dL hemoglobin and 33.3% hematocrit, bordering serum glucose 111 mg/dL and mild increase on ESR 23 mm. Transient-evoked (TE-OAE) and distortion product otoacoustic emission (DP-OAE) tests, usually used to check out the amplification function of the cochlea, disclosed any outer hair cells function confirming inner ear damage on the tested frequencies of 1.0; 1.5; 2.0; 3.0 and 4.0 kHz. Electronystagmography test, usually used to check out the function of the vestibular system, showed spontaneous nystagmus of 4°/second, with oculomotor evaluation, positioning and positional testing and caloric stimulation showing normal results. These findings suggest a mild central tonus asymmetry probably due to an associated vestibular damage. The MRI showed vascular loop on the right internal auditory canal which was considered an exam finding, not related to SHL. Despite pegylated IFN-alpha/ribavirin therapy interruption and the specific therapeutic approach to SHL there was no improvement of the hearing loss.

DISCUSSION

In most cases, SHL is severe, unilateral and idiopathic.^{1,4,6} In the United States, the incidence is 5-20 cases per 100,000 inhabitants per year.¹ Worldwide, SHL accounts for approximately 1% of all cases of deafness, and 15,000 new cases occur annually.^{7,8} Several viruses have been strongly implicated as having a causative role in the pathogenesis of SHL. Different authors have studied the incidence of seroconversion to several viruses in a group of patients presenting with SHL compared with a healthy control group.^{9,10} In the SHL group of patients, there was a significantly higher incidence of seroconversion to mumps, rubella, measles, herpes simplex, varicella-zoster, cytomegalovirus and influenza viruses types A and B. A sensory neural type of hearing loss has also been reported in patients infected with

Rickettsia rickettsii, *R. typhi* or *R. coronii*.^{11,12} Syphilis has also been frequently associated with SHL, particularly among HIV co-infected patients.^{13,14} To our knowledge hepatitis C virus has not yet been associated with SHL. This case report illustrates a rare, potentially reversible adverse reaction to pegylated IFN-alpha-2a/ribavirin combination therapy for chronic HCV infection. PEG-IFN/ribavirin treatment for chronic HCV infection has been associated with many adverse effects. Neurological adverse effects, including asthenia, vertigo, muscle cramps, cognitive impairment, irritability, depression and other psychological disorders are also frequently associated with PEG-IFN therapy.¹⁵ Rarely other neurological adverse effects of PEG-IFN therapy may include oculomotor nerve paralysis, seizures, Bell's palsy, peripheral neuropathy and acute sensorineural hearing loss.¹⁶⁻¹⁹ To the best of our knowledge, this is the first case that describes acute sensorineural hearing loss associated with PEG-IFN therapy in Brazil. Several factors may be associated with SHL in patients treated with interferon-alpha. Most studies have associated interferon-alpha rather pegylated interferon with SHL. Interferon may be directly ototoxic.²⁰ Other studies have suggested that IFN through autoimmune mechanisms could be associated with SHL.²¹ Another possible cause of SHL could be anemia. SHL has been described in patients with aplastic anemia and sickle cell anemia probably as result of intracochlear hemorrhage and vaso-occlusive or inflammatory effects.^{22,23} Our patient presented mild anemia at the time SHL was observed, however hematologic changes are common systemic side-effects in the course of PEG-IFN therapy.¹⁸ Finally, SHL in our patient could be just a coincidence. Hearing impairment increases with age and, as mentioned above, in the United States the incidence is 5-20 cases per 100,000 inhabitants per year.¹ According to a recent report SHL may occur in about 1% of chronic hepatitis C on treatment with PEG-IFN/ribavirin combination therapy.¹⁸ This rate does not differ to that observed for worldwide population incidence¹ and possible involved mechanisms include direct ototoxicity, autoimmunity, or hematological changes. In contrast to published cases on auditory disability due to standard IFN therapy, in which most patients usually recovered 7 to 14 days after the discontinuation of IFN;²¹ hearing loss may not fully resolve after discontinuation of PEG-IFN therapy.¹⁸ On the other hand, symptoms may not worsen on continued treatment. The decision whether to continue or stop treatment is not clear in the literature and should be based on the clinical judgment of the treating physician.¹⁸ In conclusion, PEG-IFN may cause SHL that may not recover after discontinuation of therapy. Immediate treatment for all possible etiologies is essential, along with targeted investigations and early referral for an ENT (Ear, Nose and Throat) specialist. Physicians should be aware of the possible ototoxic effects of IFN-PEG requiring appropriate surveillance.

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