Reversible sudden sensorineural hearing loss during chronic hepatitis C treatment with pegylated interferon/ribavirin : letter to editor

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To the Editor,

Combination of pegylated interferon alpha (PegIFNa) plus ribavirin is currently the standard therapy for patients with chronic hepatitis C (CHC). Sudden hearing loss (SHL) is a rare complication of CHC treatment that is not well documented. We report a case of a 42-year-old Greek man with CHC (genotype 1b) who developed right-sided hearing loss 46 weeks after the initiation of therapy with PegIFNa-2a subcutaneously, at a dose of 180 μg/week, and ribavirin orally, at a dose of 1200 mg/day, for a scheduled period of 48 weeks. Before treatment his clinical examination (including neurologic assessment) was normal and there was no history of previous disease or consumption of any drug or alcohol. Serum levels of glucose, urea, creatinine, electrolytes, lipids, alkaline phosphatase, gamma glutamyltransferase, bilirubin, albumin, ferritin and blood cell count were normal. Viral load was 879 063 RNA IU/ml (COBAS AMPLICOR HCV test v2.0, Roche Diagnostic Systems), alanine aminotransferase was 75 IU/L (upper limit of normal < 45) and aspartate aminotransferase was 43 IU/L (upper limit of normal < 45). Forty-six weeks after the beginning of treatment he experienced a sudden reduction of hearing ability in association with tinnitus. Three days after the onset of symptoms he was examined by an ear, nose and throat specialist. The middle ear was normal on both sides. Pulse-tone audiometry was consistent with unilateral right-sided, sensorineural hearing loss of 20~40 dB, at all frequencies. In accordance with the patient's desire to complete therapy, antiviral therapy was maintained for a further 2 week period. The patient was followed-up on an outpatient basis with weekly audiometry. Notably, he did not develop any further worsening of his hearing ability on the right side, and hearing perception on the left ear remained unaffected throughout the period of follow-up. Serum liver biochemistry was normalized during treatment and remained normal after the end of antiviral therapy. During treatment no significant hematological changes were detected and no other side effects were noted. HCV-RNA was undetectable at the end of therapy and at 24 weeks after completion of treatment. Three weeks after the onset of symptoms the patient reported a gradual improvement in hearing and complete recovery of auditory function was audiometrically documented at 5 weeks. SHL is a rare complication occurring in about 1% of patients treated with PegIFNa for CHC (1). In a prospective study by Kanda *et al.*, auditory disability (tinnitus, hearing loss or both) occurred in 32 out of 75 patients (36.6%) receiving interferon treatment (2). This side effect developed during the later stages of treatment and frequently disappeared 7-14 days after discontinuation of therapy. Multiple pathogenetic factors have been implicated in the development of interferon-induced SHL, including direct toxicity to the auditory nerve hairy cells (3,4), autoimmune mechanisms (2), and hematological changes. The role of ribavirin in the development of SHL remains unclear. To date, no cases of sensorineural hearing loss due to ribavirin monotherapy have been reported. Nonetheless, the ototoxicity of PegIFNa/ribavirin treatment has been recently challenged by a prospective study in which no impact on the hearing thresholds of 21 treated CHC patients was documented (5). However, as the authors declare, the sample size of the study was too small to demonstrate any adverse event of such rarity.

To our knowledge fourteen cases of PegIFNa/ribavirin-induced SHL have been published in the literature from 2004 to 2011 (Table 1). Mean age of affected individuals was 46.4 (SD = 11.5). Mean onset of SHL was at 19.9 (SD = 14.67) weeks of treatment (range : day 1-42 weeks). In all cases the audiometric pattern of SHL was sensorineural. In contrast to the study by Kanda *et al.* (2), other authors reported that hearing loss did not fully resolve after cessation of treatment (1,6). In the cases where recovery was noted, this took place between 10 days and 1 month after discontinuation of treatment (7,8). Maintaining therapy or re-treatment after onset of SHL has been associated with deterioration of auditory acuity (9) although this is not observed in other cases (3). In our case, SHL completely resolved 5 weeks after onset despite continuation of therapy. Only one similar case has been published by Elloumi *et al.* regarding a 47-years-old Tunisian man who developed left-sided SHL

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Table 1. — **Pegylated interferon-induced SHL during CHC treatment: Cases reported in literature from 2004 to 2011**

Author/ Country/ year	Type of treatment	Nr. of cases/ age ; sex	SHL onset	Manifestation	Management	Evolution
Formann *et al.*/ Austria/ 2004	PegIFNa-2a/2b+RBV for CHC	6 cases/ 28yo ; M 49yo ; F 55yo ; M 39yo ; M 32yo ; M 47yo ; F	1st day 4th wk 23rd wk 25th wk 36th wk 40th wk	SHL, tinnitus	Discontinuation of treatment	Hearing loss did not fully resolved after discontinuation of treatment
Elloumi *et al.*/ Tunisia/ 2007	PegIFNa-2a+RBV for CHC	1 case/ 47yo ; M	22nd wk	Otalgia, Left SHL	Continuation of treatment until week 24 (EOT)	SHL resolved 2 wks after EOT
Piekarska *et al.*/ Poland/ 2007	PegIFNa +RBV for CHC	1 case/ 27yo ; M	10th wk	Bilateral SHL	Continuation of treatment at patient's request	Slight further deterioration of hearing ability. SHL persisted 18 mo after EOT
Johnson *et al.*/ USA/ 2008	PegIFNa-2b+RBV for CHC	1 case/ 57yo ; M	2nd wk	Bilateral SHL, vertigo, tinnitus, postural intolerance	Discontinuation of treatment	Rapid clinical resolution with mild residual hearing loss
Shin *et al.*/ Korea/ 2009	PegIFNa-2b+RBV for CHC	1 case/ 60yo ; M	42nd wk	Right SHL, tinnitus	Discontinuation of treatment – Prednisone 60 mg/day	Almost complete recovered 10 d after discontinuation
Wong *et al.*/ Canada/ 2009	PegIFNa-2b+RBV for CHC	1 case/ 45yo ; F	8th wk	Right SHL, tinnitus	Treatment discontinuation for 4 mo, then re-treatment at patient's request	Hearing loss remained 4 mo after treatment discontinuation No worsening on re-treatment
Atug *et al.*/ Turkey/ 2009	PegIFNa-2a+RBV for CHC	1 case/ 47yo ; M	32th wk	Left SHL	Discontinuation of treatment	Complete recovery 1 mo after discontinuation
Le *et al.*/ USA/ 2009	PegIFNa +RBV for CHC	1 case/ 51yo ; M	6th wk	Left SHL	Prednisone while maintaining treatment	Amelioration of hearing ability
Mendes-Corrèa *et al.*/Brazil/ 2011	PegIFNa-2a+RBV for CHC	1 case/ 65yo ; M	28th wk	Right SHL	Discontinuation of treatment – Dexamethasone 8 mg/day – pentoxifylline 1200 mg/day – vitamin A 50,000 IU/day, followed by : Dexamethasone 2 mg/intratympanic	No audiometric improvement

SHL: sudden hearing loss; PegIFN: Pegylated interferon; RBV: ribavirin; EOT: end of treatment; CHC: chronic hepatitis C; wk: week; mo: months; yo: years old.

22 weeks after beginning the same treatment (10). Tinnitus often coexists, while in some cases symptoms can be more devastating and include vertigo and postural intolerance (11). SHL is mostly unilateral, although cases of bilateral involvement have been reported (9,11). Regarding pharmaceutical management of this rare side effect, administration of prednisone at high doses (60 mg/day) has been reported to be useful in two cases (3,8). On the contrary, in a recent report, use of dexamethasone 8 mg daily for 15 days, and pentoxifylline 1200 mg plus vitamin A 50000 IU daily for 30 days, failed to improve the hearing loss, while subsequent intratympanic dexamethasone 2 mg for two weeks was also ineffective (12).

In conclusion, sudden hearing loss is a rare side effect of CHC therapy that is not always reversible. Although this is a rare occurrence, clinicians prescribing PegIFNa/ribavirin combination therapy should be aware of this potential complication. The decision whereas to maintain treatment is up to the clinicians' judgment in each individual case and the patient's consent and should be the subject of a risk/benefit consideration.

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