

# Reversible sudden hearing loss in a chronic hepatitis C patient who achieved a sustained response to antiviral re-treatment

***Improvvisa e reversibile perdita dell'udito in un paziente con epatite cronica C e risposta sostenuta al trattamento antivirale***

Rosa Zampino<sup>1</sup>, Giuseppe Costa<sup>2</sup>, Mariarosaria Barillari<sup>2</sup>, Luigi Elio Adinolfi<sup>1</sup>, Aldo Marrone<sup>1</sup>

<sup>1</sup>Department Internal Medicine and Hepatology;

<sup>2</sup>Division of Phoniatry and Audiology, Second University of Naples, Naples, Italy

## INTRODUCTION

Hepatitis C virus (HCV) has been associated with hepatic and extra-hepatic manifestations, some of them peculiar [1].

Acute and chronic hepatitis C has been treated with alpha interferon with diverse results in different patients populations [2, 3].

Chronic hepatitis C is currently treated with pegylated-interferon (PEG-IFN) alpha and ribavirin and this treatment may cause local and systemic side effects [4-6].

Few cases of hearing loss during chronic hepatitis therapy with standard or PEG-IFN alpha and ribavirin have been described [7-14].

Different outcomes of the auditory disability have been reported in these patients independently of stopping antiviral treatment or starting support steroid treatment, but little information on the liver disease follow-up has been reported [10-14].

We describe the case of a chronic hepatitis C patient who received standard and PEG-IFN alpha and ribavirin and developed a reversible hearing loss during the first PEG-IFN + ribavirin treatment; he finally showed a very favorable hepatic outcome with sustained viral clearance after re-treatment.

## CASE REPORT

A 60-year-old Italian man with chronic hepatitis C for at least 20 years attended our Unit of Internal Medicine and Hepatology. He also presented peptic ulcer previously treated with PPI and had been a heavy smoker and alcohol abuser until about two years before our observation.

He refused liver biopsy and after a follow-up period of 6 months started treatment with PEG-IFN alpha 2b subcutaneously (100 mg/week) and ribavirin (1000 mg/day). Before treatment his laboratory tests showed alanine aminotransferases (ALT) 4.5 times the upper normal value, platelet count 99,000/mmc, HCV RNA  $3.8 \times 10^5$  UI/ml (Taqman<sup>®</sup> HCV, Roche S.p.a., Segrate, Milano) and HCV genotype 1b (Versant HCV genotype Assay, Innogenetics, Gent, Belgium), while other liver function tests and hematological tests were normal.

After 4 weeks of treatment the ALT values were normal and HCV RNA had dropped by >2 log versus the basal value; the patient also showed mild anemia and a lower platelet count and developed fatigue and a sudden left hearing loss. He was promptly examined by an otolaryngologist. He had not presented recent flu-like

symptoms or infections of the upper respiratory tract in the previous month. Otoscopic examination was bilaterally normal. Tympanometry was normal and stapedial reflex (ipsi - contra) was present.

Pure tone audiometry showed left sensorineural hearing loss at 500-4000 Hz frequency, threshold 45 dB.

At the same time antinuclear, anti-mitochondrial, anti smooth muscle, anti-liver kidney microsome 1 antibodies and anti-endothelial cell antibodies were negative.

Interferon treatment was discontinued and after 6 days, hearing loss disappeared; a new audiometric test performed after another six days showed a complete recovery of the hearing loss. ALT returned to the basal values within two weeks of discontinuation.

To decrease the development of side effects, five months later the patient was treated with leukocyte interferon-alpha subcutaneously (Alfaferone, Alfa Wassermann, Milan, Italy, 3MU/ 3 times a week), which is less frequently accompanied by side effects, and ribavirin (1000 mg/day) for 6 months, but no biochemical or virological response was achieved, and no hearing problems or other side effects were present (15). After three months of follow-up, the patient restarted treatment with PEG-IFN alpha-2b subcutaneously (100 mg/week) and ribavirin (1000 mg/day). During the treatment, he did not present a new episode of hearing loss, but again showed mild anemia and a low platelet count. Otolaryngology examination and audiometry test were performed every 3 months during treatment and no new hearing loss appeared.

He was treated for 48 weeks and obtained a biochemical and virological response (ALT normal and HCV RNA undetectable). After 7 years of follow-up, this patient maintains a sustained biochemical and virological response. His hearing has been monitored once a year and no hearing loss has appeared.

## ■ DISCUSSION

Hearing loss during treatment with interferon and ribavirin has been correlated to different possible causes such as a direct toxic effect, anemia, and autoimmunity activation [7, 8, 16].

The case described was a difficult-to-treat chronic hepatitis C patient due to advanced age, a long history of liver disease, HCV genotype and elevated viral load. Despite these neg-

ative predictive factors of response to antiviral therapy, he showed a sustained virological response after a full-treatment course. The emergence of hearing loss during his first treatment and the consequent premature discontinuation of therapy probably caused therapy failure. The premature discontinuation of treatment alone led to a complete resolution of the audiology disorder without any specific treatment, which was avoided due to the presence of the liver disease. The otolaryngology examinations and the favorable follow-up oriented the specialist to a direct toxic effect of treatment, perhaps in a particular moment of the patient's history. Previous experimental and clinical studies show that interferon may cause reversible changes in the cochlea, both metabolic or biochemical, and may explain the possible speedy recovery after discontinuation [7, 8, 17].

It is possible that pegylation of interferon can favor an audiological disorder, regardless of the pegylation structure ( $\alpha$ -2a or  $\alpha$ -2b interferon) [10]. In our case, it is not clear if PEG-IFN was responsible for the hearing loss, or why it did not appear during or after the second treatment. In any case, the common causes of hearing damage, such as autoimmunity and anemia, were excluded or were not so important as to justify the symptoms. A previous case of interferon-ribavirin re-treatment without signs of new hearing loss has been described [11].

These anecdotal cases of hearing loss associated to interferon-ribavirin treatment did not find confirmation in a recent prospective study evaluating hearing function before, during and after treatment with interferon and ribavirin in patients with chronic hepatitis C [18].

Despite the results of the latter study and the low incidence of hearing loss reported in the literature, it may be useful to monitor the audiology function before and during antiviral treatment with pegylated interferon and ribavirin, and promptly discontinue therapy to avoid permanent damage if hearing loss appears. Checking the audiology function may allow antiviral treatment to be re-started and possibly achieve a sustained virological response as occurred with this patient.

*Keywords:* sudden hearing loss, interferon, chronic hepatitis C.

*Conflict of interest:* The authors declare that they have no conflict of interest related to the publication of this manuscript.

## SUMMARY

We describe the case of a patient with chronic hepatitis C treated with standard and pegylated-interferon (PEG-IFN) alpha and ribavirin. He developed a reversible hearing loss during the

first course of PEG-IFN + ribavirin, but achieved sustained viral clearance and biochemical normalization after PEG-IFN + ribavirin re-treatment.

## RIASSUNTO

Descriviamo il caso di un paziente con epatite cronica da HCV sottoposto a multipli trattamenti di interferone (IFN) alpha standard o pegylato e ribavirina. Durante il primo trattamento con IFN pegylato e riba-

virina sviluppò una perdita di udito reversibile. Dopo un secondo trattamento con IFN pegylato e ribavirina ottenne stabile remissione biochimica e virologica senza danno uditivo.

## REFERENCES

- [1] Annunziata P., Marroni M., Francisco D., Stagni G. Acute transverse myelitis and hepatitis C virus. *Le Infezioni in Medicina* 1, 45-47, 2005.
- [2] Luchi S., Ricciardi L., Meini M., et al. Acute hepatitis C infection: epidemiological and clinical aspects, and efficacy of interferon therapy. *Le Infezioni in Medicina* 2, 93-98, 2007.
- [3] Alessi N., Freni M.A., Spadaro A., et al. Efficacy of interferon treatment (IFN) in elderly patients with chronic hepatitis C. *Le Infezioni in Medicina* 4, 208-212, 2003.
- [4] Ghany M.G., Strader D.B., Thomas D.L., Seeff L.B. American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 9, 1335-1374, 2009.
- [5] Sulkowski M.S., Cooper C., Hunyady B., et al. Management of adverse effects of Peg-IFN and ribavirin therapy for hepatitis C. *Nat. Rev. Gastroenterol. Hepatol.* 8, 212-223, 2011.
- [6] Rossi C., Scotton P.G., Farina F., Vaglia A. Retinopathy in chronic hepatitis C patients during interferon treatment: a case report. *Le Infezioni in Medicina* 4, 267-269, 2010.
- [7] Kanda Y., Shigeno K., Kinoshita N., Nakao K., Yano M., Matsuo H. Sudden hearing loss associated with interferon. *Lancet* 343, 1134-1135, 1994.
- [8] Kanda Y., Shigeno K., Matsuo H., Yano M., Yamada N., Kumagami H. Interferon-induced sudden hearing loss. *Audiology* 34, 98-102, 1995.
- [9] Adoni G., Marinelli L., De Santis A., Romito A., Manna R., Ottaviani F. Sudden hearing loss in a patient hepatitis C virus (HCV) positive on therapy with alpha-interferon: a possible autoimmune-microvascular pathogenesis. *J. Laryngol. Otol.* 112, 962-963, 1998.
- [10] Formann E., Stauber R., Denk D.M., et al. Sudden hearing loss in patients with chronic hepatitis C treated with pegylated interferon/ribavirin. *Am. J. Gastroenterol.* 99, 873-877, 2004.
- [11] Wong V.K., Cheong-Lee C., Ford J.A., Yoshida E.M. Acute sensorineural hearing loss associated with peginterferon and ribavirin combination therapy during hepatitis C treatment: outcome after resumption of therapy. *World J. Gastroenterol.* 11, 34, 5392-5393, 2005.
- [12] Shin M.K., Kim T.H., Ju K., et al. A case of sudden-onset hearing loss in a patient treated with peginterferon alpha-2b and ribavirin for chronic hepatitis C. *Korean J. Hepatol.* 15, 370-374, 2009.
- [13] Le V., Bader T., Fazili J. A case of hearing loss associated with pegylated interferon and ribavirin treatment ameliorated by prednisone. *Nat. Clin. Pract. Gastroenterol. Hepatol.* 6, 57-60, 2009.
- [14] Mendes-Corrêa M.C., Bittar R.S., Salmito N., Oiticica J. Pegylated interferon/ribavirin-associated sudden hearing loss in a patient with chronic hepatitis C in Brazil. *Braz. J. Infect. Dis.* 15, 87-89, 2011.
- [15] Adinolfi L.E., Durante-Mangoni E., Salzillo M., et al. Leukocyte interferon-alpha and ribavirin for treatment of chronic hepatitis C patients intolerant to pegylated-interferon. *Intern. Emerg. Med.* 4, 485-490, 2009.
- [16] Ogawa K., Kanazaki J. Aplastic anemia and sudden sensorineural hearing loss. *Acta Otolaryngol.* 514, 85-88, 1994.
- [17] Akyol M.U., Sarac S., Akyol G., et al. Investigation of the ototoxic effects of interferon alpha2A on the mouse cochlea. *Otolaryngol. Head Neck Surg.* 124, 107-110, 2001.
- [18] Hagr A., Jamjoom D., Sanai F.M., Al Hamoudi W., Abdo A.A., Al-Arfaj A. Effect of interferon treatment on hearing of patients with chronic Hepatitis C. *Saudi J. Gastroenterol.* 2, 114-118, 2011.