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Sudden hearing loss in a patient hepatitis C virus (HCV) positive on therapy with alpha-interferon: a possible autoimmune-microvascular pathogenesis

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Abstract
Alpha interferon (α-IFN) is used for the treatment of various systemic disorders. Side-effects of α-IFN therapy can involve numerous organ systems, but sudden hearing loss has only once been recorded. We report a case of sudden hearing loss occurring in a patient with chronic hepatitis C treated with α-IFN and recovered five days after the discontinuation of this agent. This is the first record of anti-endothelial cell antibodies detection in a patient with sudden hearing loss. The finding of anti-endothelial cell antibodies suggests an association between sudden hearing loss and microvascular damage during interferon therapy.

Key words: Hearing loss, sensorineural; Interferon, alpha; Endothelium; Antibody formation

Introduction

Interferon acts as a direct antiviral agent by regulating the functions of many cells of the immune response system. It plays a role in both the initial response to acute viral infection, and in maintaining and regulating the immune response. The antiviral immune response may also lead to autoimmune pathological consequences, mediated by antibodies formed in response to viral infection, or by immune complexes produced during an infection. Other autoimmune manifestations of infection also occur through other mechanisms which are still unclear (Tinghitella, 1990; Miossec, 1997).

Alpha interferon (α-IFN) therapy has been widely used for the treatment of many systemic disorders including acute and chronic viral illness (Woo and Burnakis, 1997), autoimmune diseases (Alonso and Medenica, 1995; Soos and Johnson, 1995) and neoplasms (Krown *et al.*, 1983; Quesada *et al.*, 1985; Sertoli *et al.*, 1989; White *et al.*, 1989; Skalla, 1996). The common side-effects associated with its use include a flu-like syndrome, as well as haematological, infectious, autoimmune, and psychiatric problems (Chung and Older, 1997; Dusheiko, 1997), but auditory complications of α-IFN administration are very rare (Kanda *et al.*, 1994; Kanda *et al.*, 1995). We report a case of sudden hearing loss induced by interferon that was recovered five days after its discontinuation, in which the presence of anti-endothelial cell antibodies suggest a microvascular pathogenesis.

Case report

A 62-year-old Caucasian woman with chronic hepatitis C, and treated for 15 days with 5 MU of α-IFN by daily intramuscular injection, presented with a sudden right hearing loss with tinnitus. Audiometry showed a moderate sensorineural hearing loss sloping at high frequencies (Figure 1). Her eardrum and tympanometric results were normal. No vestibular dysfunction was found. Because of liver disfunction, no steroids were prescribed. α-IFN therapy was discontinued because no other potential causes of sensorineural hearing loss were found. After five days, hearing spontaneously recovered and the tinnitus disappeared. Immunological examination (cryoglobulins, anti-nuclear, anti-smooth muscle antibodies, and immunocomplexes) was normal, except for the presence of anti-endothelial cells antibodies, detected on rat kidney tissue sections by indirect immunofluorescence (Tan and Pearson, 1972).

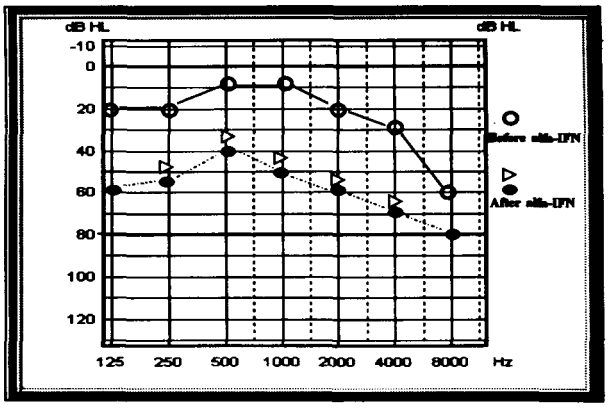

FIG. 1
The audiogram shows the sudden right sensorineural hearing loss occurring after 15 days of 5 MU of α-IFN daily intramuscular injection treatment. Five days after discontinuation of α-IFN, the hearing recovered.

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Discussion

Hepatitis C virus (HCV) infection has been associated with a plethora of immune and autoimmune disturbances, sometimes first triggered by HCV infection and then aggravated by the immunomodulatory action of interferon therapy (Hadziyannis, 1997). In fact, with the increasing long-term use of interferon (IFN) in chronic hepatitis C, numerous autoimmune problems have been recognized, such as thyroid disease (Lisker-Melman *et al.*, 1992), type 1 diabetes mellitus (Fabris *et al.*, 1992), and others (Hadziyannis, 1997). The sudden auditory disability during IFN therapy was previously observed only by Kanda *et al.* (Kanda *et al.*, 1995), who conducted a prospective study to assess the auditory function in 73 patients receiving IFN. They observed auditory disability in 17/35 patients treated with β-IFN (including hearing loss in 13 patients), and in 15/38 patients treated with α-IFN. Hearing loss and tinnitus disappeared in all patients within seven to 14 days after discontinuation of IFN. They suggest that several different mechanisms may be involved such as a microvascular damage, which was also reported in retinal vascular lesions by α-IFN therapy (Guyer *et al.*, 1993). Moreover, IFN is reported to inhibit the motility of capillary endothelial cells (Brouty-Boye and Zetter, 1980), and to induce the expression of HLA antigens (Stiem, 1982), and of autoimmune T cells through the induction of intracellular adhesion molecule-1 (Chakrabarti *et al.*, 1996).

In our report the cumulative dose until development of the sudden hearing loss was 75 MU, and five days after drug discontinuation the hearing recovered and the tinnitus disappeared. A direct ototoxicity is unlikely, while it may be hypothesized that autoimmunity precipitated or probably exacerbated by IFN therapy in an HCV-positive patient is a possible mechanism in the pathogenesis of microvascular damage. Moreover, as in ocular autoimmune disease, the microvascular damage may be monolateral (Bykovskaia *et al.*, 1997; Lyons and Rosenbaum, 1997) and the finding of autoantibodies against the endothelial cells supported our hypothesis. Other autoimmune manifestations of HCV infection also occur through mechanisms that are not clear. For instance, viral antigens could mask normal antigens or certain viral epitopes could evoke a specific sensitization that cross-reacts with a homologous sequence in the host's target antigen.

We conclude that in HCV-positive patients being treated with IFN, who complain of hearing loss and tinnitus during the therapy, IFN treatment should be withdrawn and an autoimmune-microvascular pathogenesis should be excluded, through the detection of anti-endothelial cells antibodies.

References

Alonso, K., Medenica, R. (1995) Immunomodulation in the treatment of multiple sclerosis and amyotrophic lateral sclerosis: a model for autoimmune disorders. *Journal of National Medical Association* **87:** 561–568.

Brouty-Boye, D., Zetter, B. R. (1980) Inhibition of cell motility by interferon. *Science* **208**: 516–518.

Bykovskaia, G. N., Slepova, O. S., Krichevskaia, G. I., Katargina, L. A., Kushnir, V. N. (1997) Study of antibodies to DNA in patients with bilateral and unilateral endogenous uveitis. *Vestnik Ophthalmology* **113:** 30–32.

Chakrabarti, D., Hultgren, B., Stewart, T. A. (1996) IFN-alpha induces autoimmune T cells through the induction of intracellular adhesion molecule-1 and B7.2. *Journal of Immunology* **157:** 522–528.

Chung, A., Older, S. A. (1997) Interferon-alpha associated arthritis. *Journal of Rheumatology* **24:**1844–1845.

Dusheiko, G. (1997) Side effects of alpha interferon in chronic hepatitis C. *Hepatology* **26 (Suppl):** 112–121.

Fabris, P., Betterle, C., Floreani, A., Greggio, N. A., de Lazzari, F., Naccarato, R., Chiaramonte, M. (1992) Development of type 1 diabetes mellitus during interferon alfa therapy for chronic HCV hepatitis. *Lancet* **340:** 548.

Guyer, D. R., Tiedman, J., Yannuzzi, L. A. (1993) Interferon-associated retinopathy. *Archives of Ophthalmology* **111:** 350–356.

Hadziyannis, S. J. (1997) The spectrum of extrahepatic manifestations in hepatitis C virus infection. *Journal of Viral Hepatitis* **4:** 9–28.

Kanda, Y., Shigeno, K., Kinoshita, N., Nakao, K., Yano, M., Matsuo, H. (1994) Sudden hearing loss associated with interferon. *Lancet* **343:** 1134–1135.

Kanda, Y., Shigeno, K., Matsuo, H., Yano, M., Yamada, N., Kumagami, H. (1995) Interferon-induced sudden hearing loss. *Audiology* **34:** 98–102.

Krown, S. E., Real, F. X., Cunningham-Rundles, S., Myskowski, P. L., Koziner, B., Fein, S., Mittelman, A., Oettgen, H. F., Safai, S. (1983) Preliminary observations of the effects of recombinant leukocyte and interferon in homosexual men with Kaposi's sarcoma. *New England Journal of Medicine* **308:** 1071–1076.

Lisker-Melman, M., Di Bisceglie, A. M., Usala, S. J., Weintraub, B., Murray, L. M., Hoofnagle, J. H. (1992) Development of thyroid disease during therapy of chronic viral hepatitis with interferon alfa. *Gastroenterology* **102:** 2155–2160.

Lyons, J. L., Rosenbaum, J. T. (1997) Uveitis associated with inflammatory bowel disease compared with uveitis associated with spondyloarthropathy. *Archives of Ophthalmology* **115:** 61–64.

Miossec, P. Cytokine-induced autoimmune disorders (1997) *Drug Safety* **17:** 93–104.

Quesada, J. R., Rios, A., Swanson, D., Trown, P., Gutterman, J. U. (1985) Anti-tumor activity of recombinant-derived interferon alpha in metastatic renal cell carcinoma. *Journal of Clinical Oncology* **3:** 1522–1528.

Sertoli, M. R., Bernengo, M. G., Ardizzoni, A., Brunetti, I., Falcone, A., Vidili, M. G., Cusimano, M. P., Appino, A., Doveil, G., Fortini, C. (1989) Phase II trial of recombinant alpha-2b interferon in the treatment of metastatic skin melanoma. *Oncology* **46:** 96–98.

Skalla, K. The interferons (1996) *Seminars in Oncology Nursing* **12:** 97–105.

Soos, J. M., Johnson, H. M. (1995) Type I interferon inhibition of superantigen stimulation: implications for treatment of superantigen-associated disease. *Journal of Interferon Cytokine Research* **15:** 39–45.

Stiem, E. R. (1982) Interferon: immunobiology and clinical significance. *Annals of International Medicine* **96:** 80–93.

Tan, E. M., Pearson, C. M. (1972) Rheumatic disease sera reactive with capillaries in the mouse kidney. *Arthritis and Rheumatology* **15:** 23–28.

Tinghitella, T. J. (1990) Pathogenesis of viral infections: the role of the immune response. *American Journal of Otolaryngology* **11:** 309–312.

White, C. W., Sonheimer, H. M., Crouch, E. C., Wilson, H., Fan, L. L. (1989) Treatment of pulmonary hemangiomatosis with recombinant interferon alfa-2a. *New England Journal of Medicine* **320:** 1197–1200.

Woo, M. H., Burnakis, T. G. (1997) Interferon alpha in the treatment of chronic viral hepatitis B and C. *Annals of Pharmacotherapy* **31:** 330–337.

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