Hantavirus infection: A possible cause of delayed sensorineural hearing loss

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Sensorineural hearing loss as a sequel of hantavirus infection has never been reported in the literature. Hantavirus pulmonary syndrome (HPS), a severe and often lethal respiratory disease, is caused in North America by a virus transmitted by rodents, particularly the deer mouse, *Peromyscus maniculatus*.[1-3] A previously unrecognized strain of hantavirus, now called Sin Nombre ("Virus without a name") or "Four Corners Virus (FCV)" was first identified after a cluster of deaths amongst the Navajo Indians in the four corners region of the American Southwest in 1993.[2,4-6] As of June 1995, the number of cases had grown to 110 in 23 states and 11 in Canada; 5 in British Columbia, and 6 in Alberta (Personal communication, Denise Worker, Federal Field Epidemiologist, B.C. Center for Disease Control, 1995), with about half the victims dying soon after contracting the disease.[2] Interestingly, local American Indian oral history describes three cycles of similar episodes during the twentieth century when clusters of deaths occurred in association with identifiable ecologic markers.[6,7] We present a case of severe bilateral sensorineural hearing loss in a patient who survived HPS.

CASE REPORT

A 42-year-old, previously healthy officer in the Canadian Armed Forces was on a training exercise with his troops in June 1990 in the Wainwright, Alberta training area when he started complaining of some joint aches and pains. On June 18, 1990, he experienced nausea, vomiting and extreme shortness of breath. He was admitted to his field hospital, intubated, and then transferred to the University hospital in Edmonton, Alberta. His health up to that point had been excellent and he had always been extremely fit, often running up to 10 miles every morning.

He remained in the intensive care unit in Edmonton until August 26, 1990, during which time a number of studies were done. No specific causative agent was detected and he was told he had acute respiratory distress syndrome, probably the result of a viral pneumonia. He underwent several bronchoscopies, a lumbar puncture, a computed tomography scan, and a lung biopsy, as well as several other tests and procedures, including a tracheotomy. He was treated with a number of potentially ototoxic drugs, including streptomycin, tobramycin, amikacin, and gentamicin. The serum levels of the aminoglycosides were monitored and apart from a single dose of gentamicin, all serum levels were well within the safety margin.

After discharge from the intensive care unit, he remained on a pulmonary ward for 3 weeks and was then transferred to Victoria, where after 2 weeks in a pulmonary ward, he was discharged home. He continued to have excessive fatigue and weakness at home and was therefore admitted to a military hospital for the month of October 1990.

On January 27, 1991, almost 5 months after discharge from the intensive care unit and 2 weeks after stopping coumadin, which he was taking for a deep vein thrombosis, a hissing tinnitus developed in his right ear that was followed a few weeks later by a similar complaint in the left ear. He also noticed that his hearing had deteriorated during this period. An audiogram done on January 31, 1991, revealed a high tone hearing deficit in both ears, with the right ear being worse than the left (Fig. 1). A second audiogram done on February 26, 1991, showed a slightly worse hearing loss, with the right ear still being worse than the left (Fig. 2). In March 1991, a neurologic evaluation and a computed tomography scan of the internal auditory canals were done and revealed no abnormalities.

The patient was seen in the Ear Nose and Throat clinic at Vancouver Hospital and Health Sciences Center on March 15, 1991, at which time a full examination was carried out. Several tests, including electronystagmography, auditory brain stem responses, tympanograms, and blood tests were performed to rule out autoimmune or luetic disorders. All the results were within normal limits. An audiogram done in April 1991 showed worsening hearing loss at the high frequencies in both ears, with the right ear remaining worse (Fig. 3) than the left ear. Over the subsequent 12 months, the hearing of the patient slowly deteriorated. During this time, no vestibular symptoms were noticed by the patient.

He was referred for a second opinion to a U.S. clinic in August 1992, where a second audiogram showed a further deterioration in hearing in both ears, with the right one again being worse than the left (Fig. 4). By this time, the patient had been fitted with hearing aids. He received a 2-month, gradually tapering dose of prednisone but his condition showed no improvement.

A follow up visit in Vancouver on February 1, 1993, showed a mild hearing loss of 250 Hz sloping to a flat, moderate to severe sensorineural hearing loss above 500 Hz on the right side, and normal hearing at 250 Hz with a moderate to severe sensorineural hearing loss above 500 Hz on the left side (Fig. 5). The results of further audiograms after this have remained unchanged.

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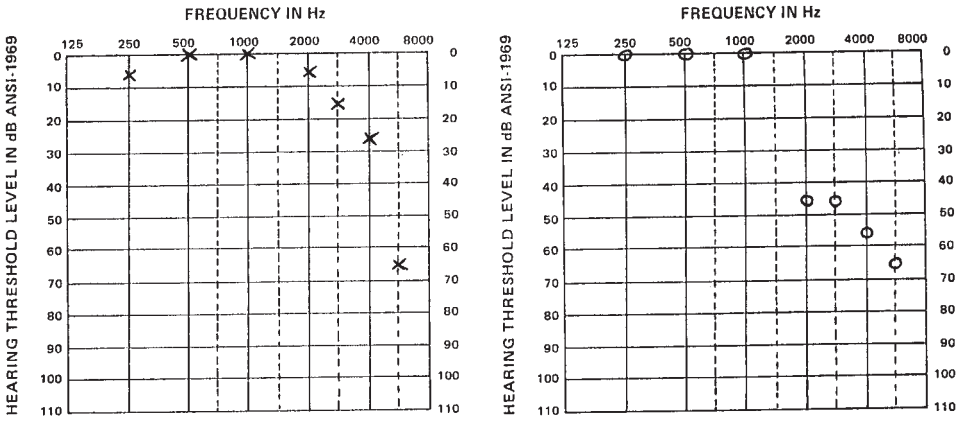

Fig. 1. Audiogram from January 31, 1991.

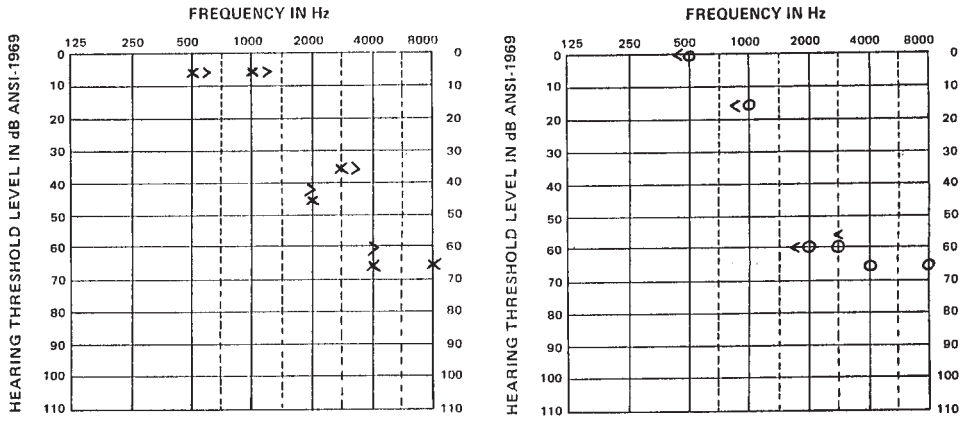

Fig. 2. Audiogram from February 26, 1991.

Interestingly, by mid-1994 the patient had read about and researched the well publicized outbreak of severe respiratory illness in the southwest United States caused by hantavirus that had claimed several lives. Noting the similarity in the illness caused by the hantavirus to his own illness, he questioned the initial diagnosis given to him about his illness. He brought this to the attention of the doctors who had treated him while he was in the intensive care unit. A biopsy sample of the lung taken at the time of his illness was forwarded to the Centers for Disease Control in Atlanta, Georgia, where the diagnosis of hantavirus infection was confirmed. An accompanying correspondence report stated, "We have never seen such extensive histopathologic changes in lung tissue of a patient that has survived Hantavirus Pulmonary Syndrome." The belated diagnosis of HPS was therefore a patient discovery after discharge from the hospital when he was relatively healthy, in fact after most of the hearing loss had occurred.

DISCUSSION

The HPS of this patient was described in a previous publication but the loss of hearing that developed later was not mentioned.[8] Possible explanations for the development of hearing loss in this healthy adult man are: 1) delayed effect of aminoglycosides; 2) hereditary progressive hearing loss; 3) effect of hantavirus infection; or 4) possible embolic phenomena.

Aminoglycoside ototoxicity is well documented in the literature and has been one of the major limitations of the usefulness of aminoglycosides.[10,11,12,27] Cochleotoxicity, vestibulotoxicity, or both can occur in patients receiving aminoglycosides.[13,27] Cochleotoxicity can occur despite "safe" drug levels and in the absence of nephrotoxicity. Most aminoglycosides also have been shown to be able to cause delayed cochleotoxicity that begins after discontinuation of the drug.[11,14] Tinnitus is often the first sign of cochlear damage.[15] Reversibility of sensorineural hearing loss caused by aminoglycosides is a well known phenomenon and occurs 1 week to 6 months after discontinuation of therapy in up to 55% of patients.[16] Reversibility is less likely to occur if the hearing loss is greater than 25 dB. To minimize the risk of ototoxicity, one can carry out repetitive monitoring of peak and trough levels and have large intervals between doses to

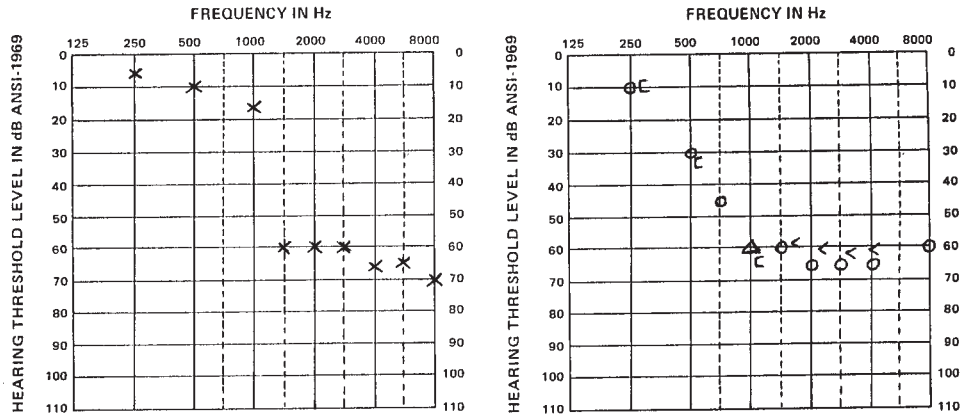

Fig. 3. Audiogram from April 5, 1991.

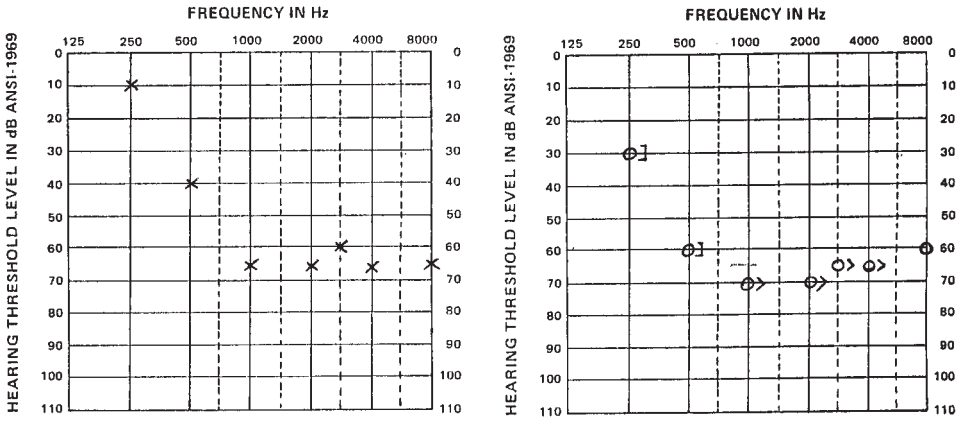

Fig. 4. Audiogram from August 17, 1992.

allow clearance from perilymph, especially in the presence of renal failure. Neither peak nor trough levels have been shown to correlate closely with ototoxicity. A closer correlation exists between the total dose resulting from the accumulation of the drug in the inner ear.[11,17,18,19] Poor renal function is an important potentiator of ototoxic effects.[17,18,20]

Aminoglycosides exert their ototoxic effect by destroying sensory hair cells in the ear. The outer hair cells in the basal turn of the cochlea are most vulnerable and ototoxicity progressively advances to the inner hair cells.[19] Aminoglycoside toxicity therefore initially affects very high frequencies, in the region of 20 kHz.[15] Damage progresses to lower frequencies with time and because humans rely on low frequencies for hearing, between 300 Hz and 3 kHz, hearing is only affected by extensive aminoglycoside-induced damage.

In our patient, the crucial question became, "At what point after discontinuation of therapy can ototoxicity occur and still be attributed to the medications?" Frequently, symptoms of hearing loss first become evident after a period of latency after withdrawal of the drug. Delayed onset of ototoxicity is often observed and has been noted to occur up to 3 weeks after the end of drug therapy.[14] Hearing loss occurring nearly 5 months after the end of treatment has never been reported to occur as a result of medications. It is therefore reasonable to assume that the hearing loss in this patient was most likely not caused by aminoglycoside toxicity.

Hereditary progressive hearing losses are usually symmetrical but also usually occur more insidiously and progress more slowly than seen in this case.

Sensorineural hearing loss can be associated with several different viruses.[10,11,21] The first virus shown to be associated with hearing loss was the virus that causes mumps.[25] In experimental studies, viral seroconversion was found in 63% of affected patients compared with 40% of the control subjects, especially for influenza B and cytomegalovirus.[22] Other significant viruses include the mumps virus, the rubella virus, and varicella zoster.[10,11,21] Hantavirus has never been reported to cause hearing loss before.

Finally, embolic phenomena should be considered as a possible cause because the patient was being treated with coumadin, which was discontinued 2 weeks before his ear symptoms began. No other neurologic symptoms, however,

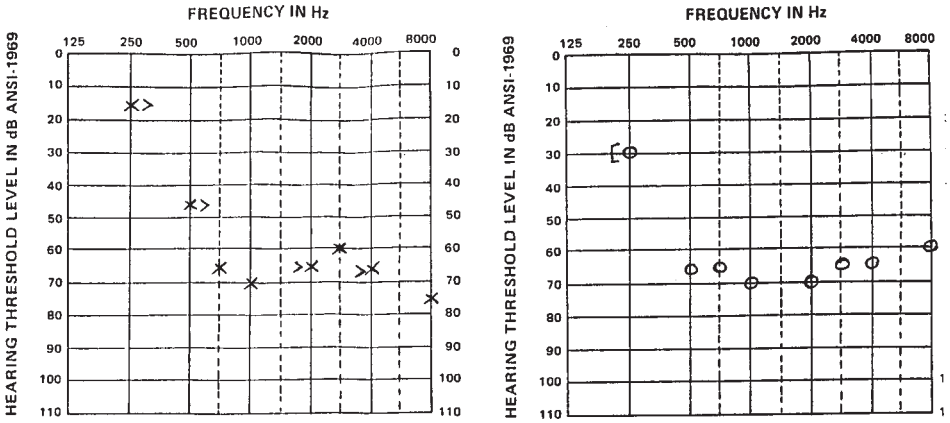

Fig. 5. Audiogram from February 1, 1993.

appeared with his otologic findings to suggest an embolic phenomenon, and the patient was fully mobile at the time. Also, the fact that both ears were affected quite symmetrically makes it unlikely that an embolic phenomenon played a role in the disease of this patient.

Hantavirus has long been identified in Eurasia as the agent responsible for Epidemic Hemorrhagic Fever (EHF), a disease process characterized by sequential periods of fever, hypotension, oliguria, and polyuria.[23,24] Inhalation of aerosolized excreta from infected rodents is the predominant mechanism of hantavirus infection.[2,23] There is no evidence of person to person transmission for any of the known hantaviruses.[23] Common disorders of the central nervous system (CNS) that are associated with EHF include confusion, lethargy, convulsions, and coma.[24] Disorders of the CNS associated with HPS have not been documented separately but currently are presumed to be no different from those associated with EHF. Studies of CNS manifestations of EHF have failed to find any evidence of an increase in sensorineural hearing loss.

Genetic studies have identified a substantial degree of genetic diversity among the hantaviruses.[5,28] It appears that the virus has the ability to attack different organs: originally the kidneys (EHF) and now the lungs (HPS). Is it possible that a novel form of the virus now has the ability to destroy the organs of hearing?

CONCLUSION

The hearing loss of this patient occurred first in the higher tones, which would be compatible with some form of toxic damage to the inner ear. The onset of the deficit, however, appeared so long after the termination of his illness, making it difficult to ascribe the cause of the hearing loss to the aminoglycosides. The onset of tinnitus at the time of his hearing loss suggests that some active process was occurring. The pattern of hearing loss seen in this patient is very unusual and is difficult to explain using one of the known causes of sensorineural hearing loss.

The purpose of publishing this case report is to draw the attention of infectious disease experts and otolaryngologists to the possibility of hearing loss caused by a hantavirus. The unusual nature of loss described here and its time course after recovery from HPS suggests that this was the causative factor. If indeed hearing loss is a part of HPS, then other cases of this pattern of hearing loss may have gone unrecognized. A description of this case may allow recognition of hearing loss caused by hantavirus in other cases. Conversely, development of this type of hearing loss in a patient who has recovered from a respiratory disorder may make serologic assessment for hantavirus and belated recognition of the pulmonary syndrome as HPS worthwhile. If no other cases come to light then perhaps the hearing loss of this patient was just an atypical, sporadic, progressive sensorineural hearing loss occurring in mid-life.

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