

Temporal Bone Histopathology of Furosemide Ototoxicity

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Objectives: To describe the human temporal bone pathology in two patients who incurred furosemide induced ototoxicity.

Patients: 1) A 46-year-old woman in acute liver and renal failure treated with high doses of furosemide for anasarca who developed a rapidly progressive severe-to-profound asymmetric sensorineural hearing loss. 2) A 65-year-old woman with undifferentiated small cell carcinoma of the lung who received intravenous furosemide 1 day prior to death for pulmonary edema.

Interventions: Removal of temporal bones, histologic processing, and light microscopy of temporal bones.

Main Outcome Measures: Temporal bone histopathology and correlation with clinical and audiometric data.

Results: All three temporal bones demonstrated edema and cystic changes in the stria vascularis. In the first case the furosemide exposure was associated with hearing loss and the pathological changes were more extensive including cystic changes in the Hensen's cells, collapse of Reissner's membrane and the tectorial membrane and diffuse loss of inner and outer hair cells with only modest reduction in the spiral ganglion cell population. In the second case, without attributable hearing loss, there was only modest reduction in hair cell and spiral ganglion cell counts. Pathological changes were not observed in the ampullae of the semicircular canals or epithelium of the saccular or utricular maculae in either case.

Conclusions: The temporal bone pathologic correlate for furosemide-induced ototoxicity is edema and cystic degeneration of the stria vascularis. The degree of degenerative change appears dose-dependent. We infer that pathological changes may occur in the absence of a measurable immediate clinical effect.

Key Words: Ototoxicity, furosemide, sensorineural hearing loss, stria vascularis.

Level of Evidence: NA.

INTRODUCTION

Ototoxicity refers to drug induced changes that affect hearing and/or balance. The loop diuretics are known to have the potential to induce hearing loss. These drugs are commonly used for the treatment of hypertension and edema. They act on the ascending loop of Henle to inhibit the resorption of sodium, chloride, and potassium. Furosemide, ethacrynic acid, and bumetanide are the most commonly prescribed loop diuretics. Sudden, progressive, reversible, and profound hearing loss have been ascribed to loop diuretics, including furosemide.¹

In human temporal bone studies, cystic changes in the stria vascularis and dark cells of the vestibular organs, and loss of inner and outer hair cells have been

observed in cases of ethacrynic acid and ethacrynic acid with concurrent furosemide exposure.²⁻⁴ Animal studies of furosemide ototoxicity have also demonstrated pathological change in the stria vascularis.^{5,6}

We describe here the temporal bone histopathology, clinical course, and audiometry of two patients with and without sensorineural hearing loss after administration of furosemide. To our knowledge, this is the first otopathology report of isolated furosemide ototoxicity.

METHODS

Clinical history and audiologic evaluations were collected during life through enrollment in the National Institute on Deafness and Other Communication Disorders (NIDCD) National Temporal Bone, Hearing, and Balance Pathology Resource Registry.

After death, the temporal bones were fixed in formalin. The temporal bones then underwent standard processing for histologic examination, including decalcification with ethylenediamine tetra-acetic acid (EDTA) and celloidin embedding. The specimens were sectioned serially in the horizontal plane at a section thickness of 20 μ m. Every 10th section was stained with hematoxylin and eosin and mounted on a glass slide. The slides were examined by light microscopy. Graphic reconstruction of the cochlea was performed to quantify hair cells, pathologic changes to the stria vascularis, and loss of cochlear neuronal cells.

RESULTS

Case 1

The patient had a history of rheumatoid arthritis. At the age of 45 she developed new onset idiopathic

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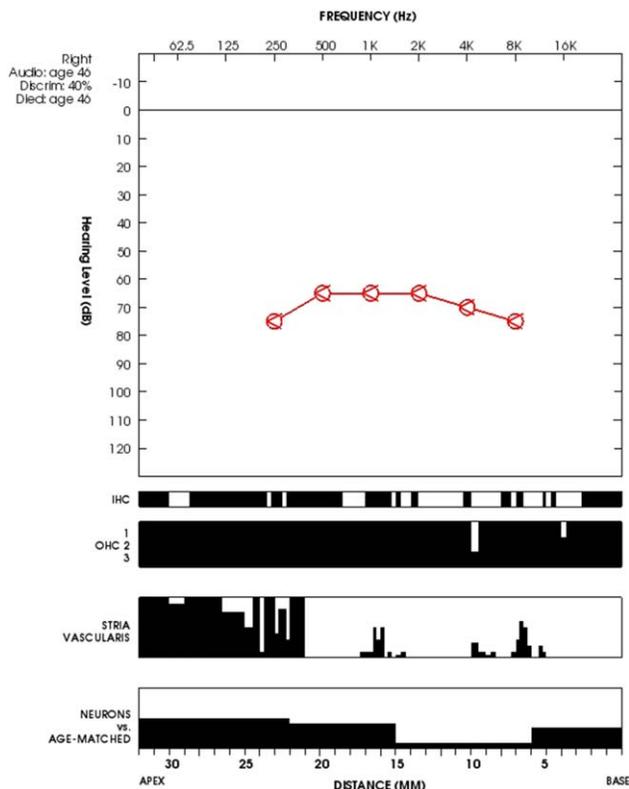


Fig. 1. Audiocytocochleogram for Case 1 Right Ear. There is a severe sensorineural hearing loss in the right ear. Speech discrimination in the right ear was 40%. In the cytochleogram black bars indicate loss and for the stria vascularis percentage of cystic change. There was severe loss of inner and outer hair cells. The stria vascularis showed cystic changes primarily in the apex. There was a 32.2% loss of spiral ganglion cells compared to aged matched controls.

anasarca, myopathy, and weight loss. She was treated with increasing doses of furosemide (up to 600 mg daily) over 9 months and began to note hearing loss in both ears. Her hearing loss progressed for 5 months during which time she was diagnosed with panniculitis. She was treated with prednisone and mepron (for *Pneumocystis jirovecii* prophylaxis) for the panniculitis. Seven weeks later she was terminally admitted in acute liver and renal failure. An audiogram showed a profound loss in the left ear and a severe flat loss in the right ear with a speech discrimination score of 40%. An MRI of the brain and internal auditory canals at the time showed no evidence of retrocochlear pathology. An autopsy revealed acute liver and renal failure with evidence of *Clostridium perfringens* bacteremia.

The histopathological findings were similar in both ears. There was severe loss of inner and all three rows of outer hair cells from the base to the apex of the cochlea as graphically represented in the cytochleogram (Figs. 1 and 2).

There was a cystic separation of the basal cells of the stria vascularis from the spiral ligament. This was associated with a partial collapse of Reissner's membrane in both cochleae, most severe at the apex. The Hensen's cells exhibited a cystic dilation from the basilar

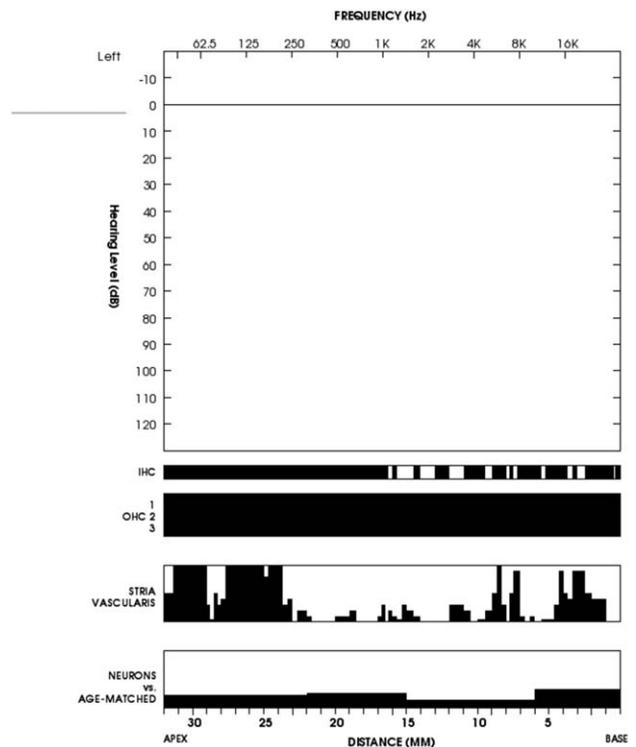


Fig. 2. Audiocytocochleogram for Case 1 Left Ear. There is a profound loss on the left prior to death. No responses were elicited from the left ear during audiometric testing. In the cytochleogram black bars indicate loss and for the stria vascularis percentage of cystic change. There was severe loss of inner and outer hair cells. The stria vascularis showed cystic changes primarily in the apex. There was a 24% loss of spiral ganglion cells compared to aged matched controls.

membrane. These findings were evident in the right (Fig. 3) and left ear (Fig. 4). There was collapse of the tectorial membrane throughout the organ of Corti. There were no pathological changes in the dark cells or hair cells of the vestibular organs.

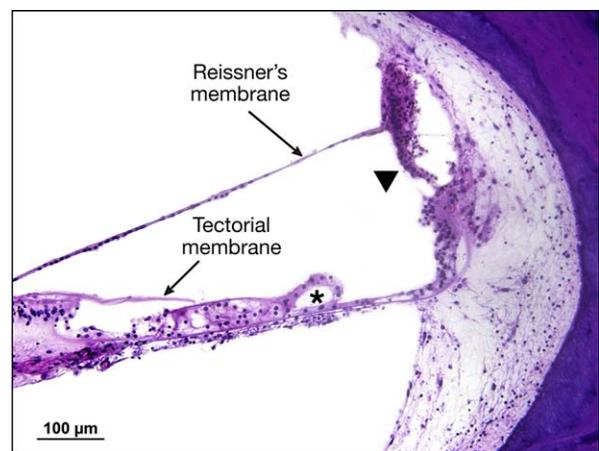


Fig. 3. Case 1. Right ear. Apical section of the organ of Corti. There is cystic separation of the stria vascularis from the spiral ligament (arrow head). Reissner's membrane and the tectorial membrane are collapsed. Hensen's cells are flattened and elevated from the basilar membrane by a cyst (asterix).

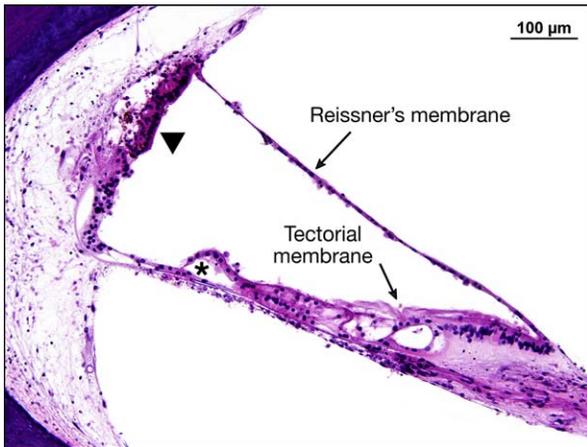


Fig. 4. Case 1. Left ear. Basal section of the left organ of Corti. There is a cystic separation of the stria vascularis from the spiral ligament (arrow head). The tectorial membrane is collapsed. Hensen's cells are flattened and elevated from the basilar membrane by a cyst (asterisk).

Compared to age matched controls there was 24% loss of spiral ganglion cells in the left ear and 32.2% on the right.

Case 2

This previously healthy woman presented at the age of 65 with pneumonia and a right hilar mass that on biopsy revealed small cell undifferentiated carcinoma. During the ensuing 3 months she received antibiotics, diuretics, chemotherapy (Adriamycin, Cytoxan and VP-16), and radiation. A baseline audiogram showed symmetric thresholds of 15 dB to 2000 Hz with a descending pattern in the high frequencies. She tolerated her treatment until she developed acute onset fatigue, fever, chills, and nausea and died several days later. In addition to the carcinoma of the lung, autopsy revealed pulmonary edema, a pleural effusion, and chronic pancreatitis. One day prior to death

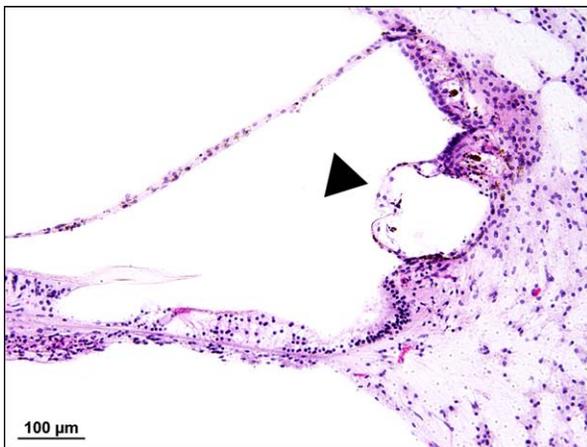


Fig. 5. Case 2. Left Ear. Upper basal turn of the cochlea. There is a cystic dilation of the stria vascularis (arrow head) above the spiral prominence. The cytoarchitecture of the organ of Corti is well preserved.

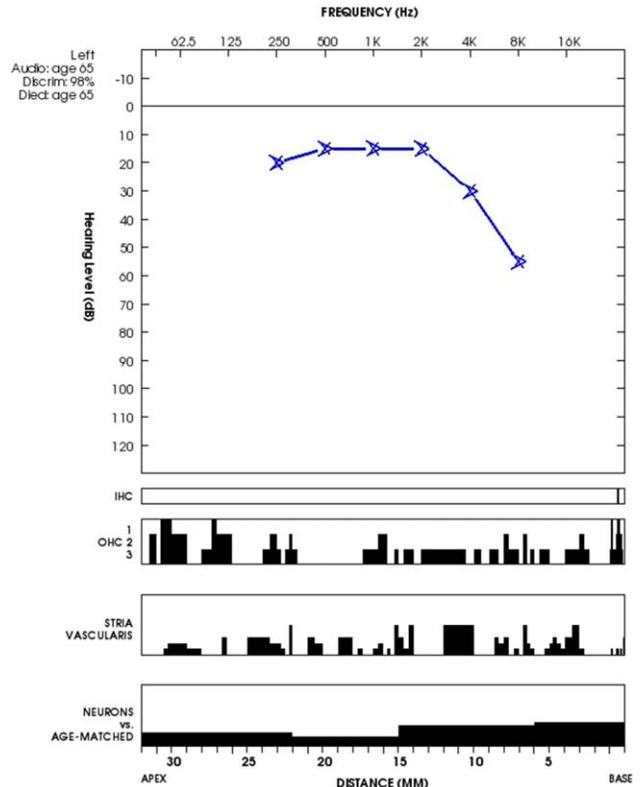


Fig. 6. Audiocytocochleogram for Case 2 left ear. There is a moderately severe to severe high frequency sensorineural above 4 Hz. Speech discrimination was normal. In the cytocochleogram black bars indicate loss and for the stria vascularis percentage of cystic change. There was minimal loss of inner and outer hair cells. The stria vascularis showed patchy cystic changes throughout the cochlea. There was a 27% loss of spiral ganglion cells compared to aged matched controls.

and 9 days following the audiogram she received 2,040 mg of furosemide.

Only the left temporal bone was available for study. The predominant feature of the ear was edema of the intermediate layer of the stria vascularis. There was cystic degeneration along the margin of the stria vascularis adjacent to the spiral prominence (Fig. 5). All three layers appeared affected. In the remainder of the stria vascularis the marginal and basal cell layers were intact. There was only modest reduction of inner and outer hair cells and spiral ganglion neurons as graphically represented in the cytocochleogram (Fig. 6). There were no pathological changes in the dark cells or hair cells of the vestibular organs. Compared to age matched controls there was 27% loss of spiral ganglion cells in the left ear.

DISCUSSION

The primary pathologic change in both cases was edema with cystic dilations in the stria vascularis. This is consistent with previous reports of human pathological changes in loop diuretic ototoxicity. Human temporal bone studies of ethacrynic acid ototoxicity have demonstrated edema in the stria vascularis, loss of outer hair

cells and cystic changes in the ampullae of the posterior canal and saccule.² Arnold et al. observed cystic dilations in the stria vascularis and dark cells of the vestibular system in patients with sudden hearing loss and ataxia after furosemide and ethacrynic acid administration.⁴ While Hensen's cell cysts as observed in case 1 have been reported in human specimens before,⁷ they have not been described in association with ototoxicity. The significance of this finding is unknown.

Edema of the stria vascularis has also been observed in animal models of furosemide ototoxicity. The primary finding of electron microscopy studies of guinea pigs following intraperitoneal injections of furosemide was enlargement of the extracellular spaces from the marginal cell tight junctions to the basal cell layer with widening of the stria vascularis.⁵ Outer hair cell damage was observed in specimens that exhibited a greater degree of stria vascularis damage. This latter finding was interpreted as being a secondary effect resulting from changes in the stria vascularis.

The clinical manifestation of loop diuretic ototoxicity is sensorineural hearing loss. The hearing loss can be reversible or maybe permanent and is often dose-dependent.¹ There was a longer exposure to furosemide in case 1 and accordingly a greater degree of injury to the stria vascularis and hair cell loss and degree of hearing loss. This patient also had renal and hepatic insufficiencies that are known to potentiate ototoxic effects.

The pharmacokinetics of loop diuretics and who is affected by ototoxicity are governed by many physiologic parameters. These drugs are highly bound to plasma protein and subject to hepatic and renal metabolism and excretion. It follows that a patient in hepatic and renal failure would be susceptible to higher concentrations of drug and therefore an increased risk of ototoxicity. Specifically, Rybak et al. have shown an increased reduction in the endocochlear potential in a low serum albumin mouse model of furosemide ototoxicity.⁸ Prior to death the albumin level in case 1 was abnormally low and liver function tests abnormally high consistent with hepatic failure.

In case 2, where only a single dose of furosemide was administered close to death, the extent of pathology of the stria vascularis was less severe and accordingly there was minimal hair cell loss. The patient died 24 hours following this administration and there was no documentation of additional hearing loss or tinnitus in the available clinical records.

The described histopathological findings supported by animal studies provide a mechanistic explanation for changes in hearing with furosemide; increasing doses of loop diuretics have an effect on the stria vascularis and could thereby reduce the endocochlear potential.⁹ The stria vascularis is known to play a role in potassium recycling for maintenance of the endolymphatic potential.¹⁰ Animal studies have also shown loop diuretics to reduce the cochlear microphonic potential¹¹ and the eighth nerve action potential.¹² Loop diuretic induced reduction in these physiologic parameters has not yet been measured in humans.

While the systemic administration of the drug in case 1 would predict a more symmetric pattern to the hearing loss, the measured asymmetry in hearing serves as an important reminder to the clinician of the variable patterns of presentation of ototoxicity given the number of potential physiologically dependent variables. The number of observed surviving spiral ganglion cell counts has been positively correlated to word recognition scores in patients with a cochlear implant during life.¹³ In case 1 the number of surviving spiral ganglion cell counts measures favorably to documented cases of patients with a cochlear implant in life who were good to excellent performers with fewer surviving spiral ganglion cells¹⁴ therefore predicting a favorable outcome for cochlear implant candidates following loop diuretic ototoxicity.

CONCLUSION

1. The primary otopathological correlate of furosemide ototoxicity is edema and cystic dilation of the stria vascularis
2. The hearing loss of loop diuretic ototoxicity may be asymmetric.
3. Renal and liver failure may increase susceptibility to loop diuretic ototoxicity.
4. Patients with severe to profound hearing loss from loop diuretic therapy may benefit from cochlear implantation.

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