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Hearing Loss and Inner Ear Changes in a Patient Suffering From Severe Gentamicin Ototoxicity

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Hörverlust und Innenohrveränderungen bei einem Patienten nach hochdosierter Gentamyzin-Applikation

Zusammenfassung. Die histologischen Veränderungen an der menschlichen Kochlea nach acht Jahre zurückliegender hochdosierter Gentamyzin-Applikation bei an Taubheit grenzender Schwerhörigkeit, werden aufgezeigt. Folge der ototoxischen Wirkung von Gentamyzin ist zunächst eine Zerstörung der Sinneszellen im Cortischen Organ, denen eine solche der Stützzellen folgt. Dann verschwinden die Nervenfasern und die Zellen im Ganglion spirale und letztlich bleibt eine dünne Zellage auf der Basilarmembran. In der Stria vascularis sind dann bei Bildung von Zysten keine Gefäße mehr nachzuweisen.

Schlüsselwörter: Gentamyzin-Ototoxizität – Hörverlust – Innenohrveränderungen

Summary. The long-term histological effects of gentamicin ototoxicity could be studied in a human being in relation to the audiometric impairment. The possible sequence of degeneration of hair cells, supporting cells, nerve fibers, stria vascularis, spiral ganglion cells, and vascular supply is discussed.

Key words: Gentamicin ototoxicity – Hearing loss – Inner ear changes

The inner ear pathology produced by aminoglucoside administration has been the subject of extensive studies by many authors. Most data were obtained in animal studies (Hawkins et al. 1969; Wersäll et al. 1969; Ylikoski et al. 1973), reports on inner ear lesions in human beings are still rare (Benitez et al. 1962; Lindsay et al. 1960; Lowry et al. 1973). In most experimental animal studies the classical inner ear cross-section technique has been used (Schuknecht 1953).

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The present study gives a report of the audiometric data and the inner ear findings in a young human patient affected with a severe gentamicin intoxication obtained by means of the s.c. surface technique (Hawkins and Johnsson 1975; Johnsson 1979).

Clinical Data

The patient, a young woman aged 24, bodyweight 31 kg, with a congenital low-thoracic meningocele and paralysis of the lower limbs developed a serious pseudomonas osteomyelitis of the pelvis and right femur in August 1970. She was treated by surgery and relatively high doses of gentamicin (180 mg daily). As the disease exacerbated immediately when, after 2 weeks, gentamicin was changed for other (non-ototoxic) antibiotics, the gentamicin administration was resumed. The disease was ultimately cured by repeated surgery and a prolonged cure of gentamicin in decreasing dosage (Fig. 1).

During the treatment the kidney function was temporarily impaired.

By the end of the therapy it was noted that a severe deafness had developed. On audiometry the patient's left ear appeared to be totally deaf and on the right side a severe high-tone sensory neural impairment and speech discrimination loss was measured. Eight months later a considerable increase of the hearing impairment was found. Since that moment hearing remained stable.

On caloric examination, the vestibular function was found to have completely ceased bilaterally.

As the patient received no other ototoxic drugs and her hearing was normal before, the lesion was attributed to gentamicin ototoxicity. Her case was described before by Huizing (1972).

Since this illness the condition of the patient remained stable until she developed an urosepsis and peritonitis in December 1978, of which she died within a few days. During her fatal illness she received 180 mg tobramicin i.v. per day for 5 days. No other ototoxic drugs were administered.

Histological Data

The right ear was microdissected and the cochlea was studied by means of the surface technique and phasecontrast microscopy. The modiolus was cross-sectioned into serial slices and was studied with light microscopy.

In the middle ear a congenital deformation of the stapes was found. The crura were considerably thickened and partially fused. The middle ear was otherwise normal and a normal stapedius tendon was present.

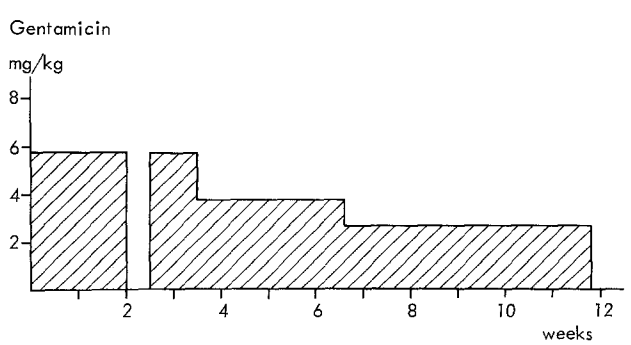


Fig. 1. Dosage of gentamicin given to patient

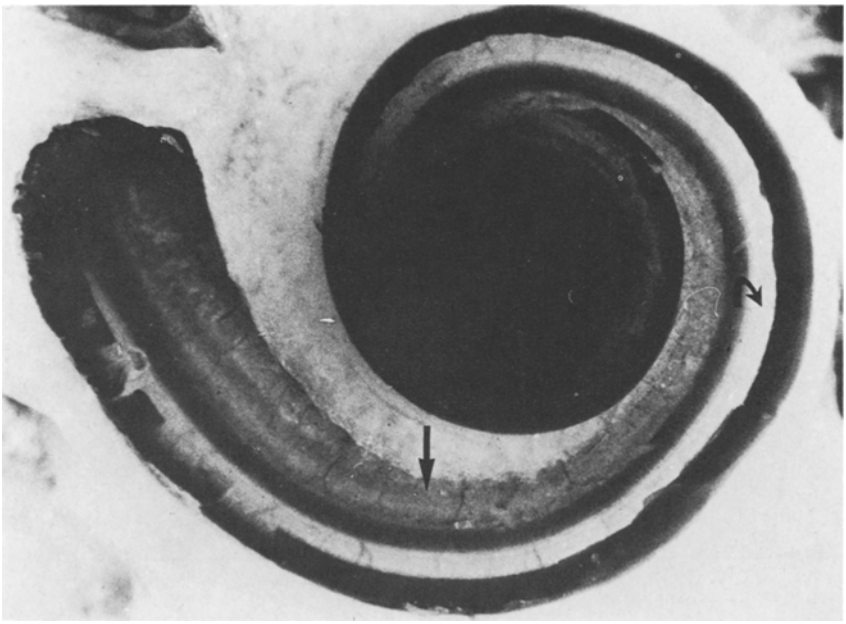


Fig. 2. Microdissected right cochlea of patient. Straight arrow: no myelinated nerve fibers in osseous spiral lamina; curved arrow: absence of spiral organ

In the inner ear a severe degeneration of almost all parts was observed in all cochlear windings (Fig. 2).

Hair Cells

Only in the first 3.3-mm range from the apex some of the hair cells and supporting cells were found intact. The percentage of intact outer and inner hair cells are given in Fig. 3a and b in combination with the threshold audiogram.

The outer hair cells had almost completely disappeared except for a very small percentage in the first 3.3 mm. About 60% of the inner hair cells were still present in this area. The audiogram showed a loss of 50 dB for frequencies under 500 Hz and total deafness above 8,000 Hz.

In the area between 3.3 and 16.5 mm from the apex all hair cells and supporting cells were destroyed. Their remnants could still partially be identified, however.

From the apex downwards a gradual decrease of the height of the cellular structures was observed.

Beyond the 16.5-mm range neither hair cell nor supporting cell remnants could be discovered. The spiral organ area was covered with a layer of large, flat, polygonal cells resting on the basilar membrane.

Figure 4 illustrates the findings above described. The righthand row of figures shows characteristic photographs of the three different areas. The left-hand row consists of drawn reconstructions of these parts.

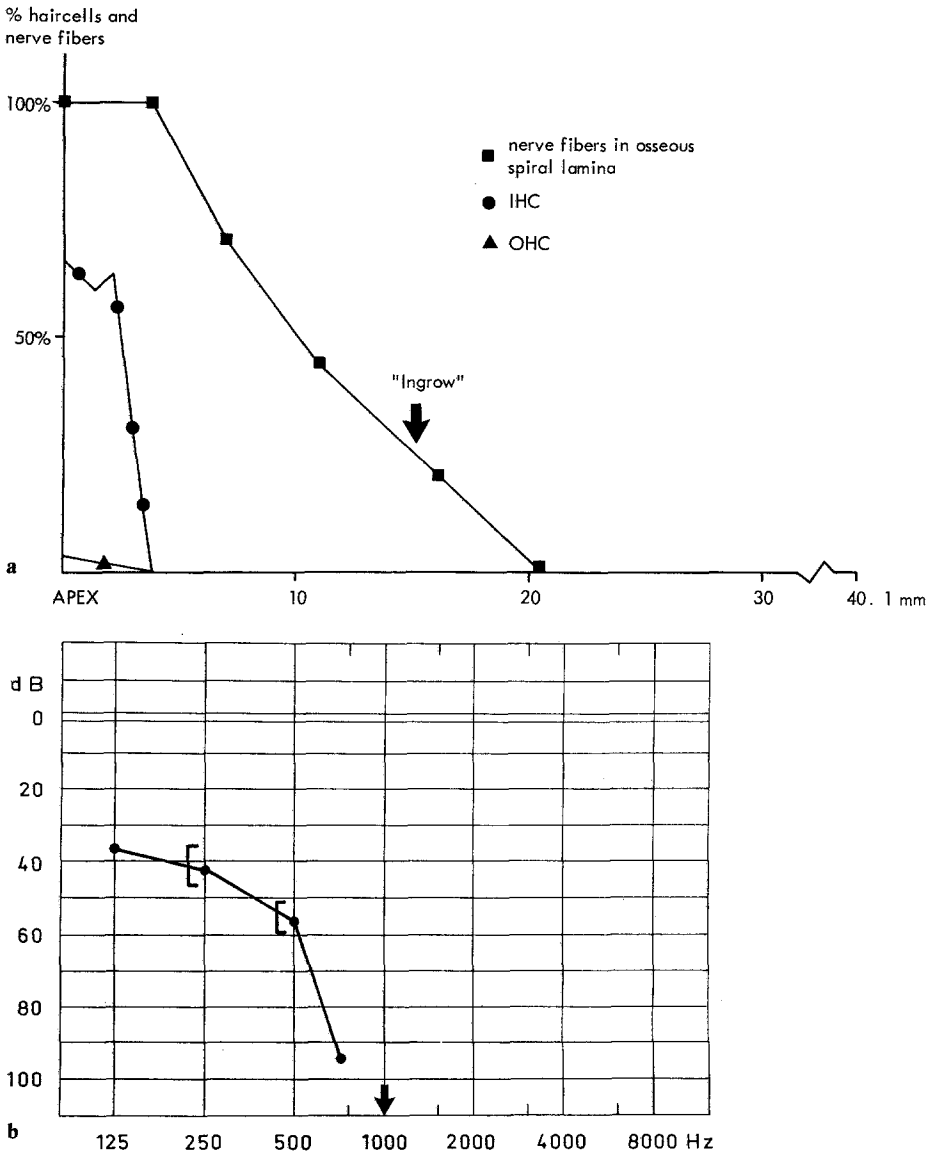


Fig. 3. **a** Cytocochleogram of right ear; **b** Audiogram of right ear

Nerve Fibers

Within the first 3.3-mm range a normal amount of myelinated nerve fibers were visible in the osseous spiral lamina. From 3.3 mm onward their number gradually diminished (Fig. 3a). In the region between 16.5 and 21 mm a number of myelinated fibers were observed which seemed to be in search of (missing) hair cells (see Fig. 5). This interesting phenomenon has also been seen in animal experiments (Terayama et al. 1977, 1979). Beyond 21 mm no nerve fibers were present.

Vascular Supply of Basilar Membrane

The vascular bed of the basilar membrane did not show any abnormality. In the basal turn a relatively great numer of anastomoses between the scala tympani vessels and the outer spiral vessel was observed. It is not clear if this has to be considered pathological.

Stria Vascularis

The stria showed a normal appearance in the apex region. In the basal coil most vessels had atrophied. In this region also several cysts were observed (Fig. 6). Some cysts were found in the 3.3 to 16.5-mm zone, whereas they were missing in the apex region.

Spiral Ganglion-Modiolus

In the apex region spiral ganglion cells can still be observed, whereas they are lacking in the middle and basal coil. The nerve fibers originating in these coils have degenerated. In animal experiments this secondary degeneration of the spiral ganglion cells after hair cell loss due to aminoglycoside intoxication has often been seen (Wicke et al. 1978). It is interesting to note that the inner spiral bundle is still visible on the level of the second turn where the nerve fibers have already disappeared (Fig. 6).

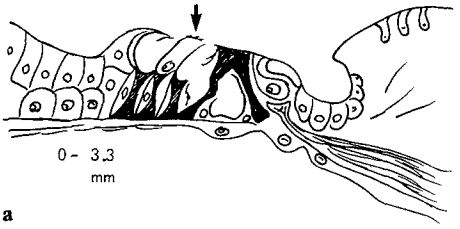
Discussion

The findings described above are most likely the late effects of a severe gentamicin-induced cochlear damage. As the patient died at the age of 33, presbyacusis will not have played a role in this case. Noise influences can also be excluded with certainty. Factors that may have played a role are hereditary influences, infections, and other ototoxic drugs. However, there is nothing to suggest this in the present case. The patient received some other potentially ototoxic drugs, but in low doses and for a short duration only.

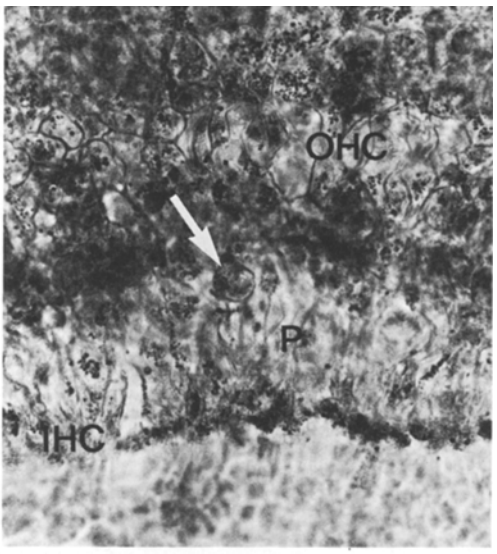
Sequence of Degeneration in the Case Described

If we assume that the findings in this case are the result of a gradual degeneration proceeding from the base to the apex, the various parts of the cochlea will represent successive stages of this process. If we accept this hypothesis, the following stages of degeneration might be distinguished:

Stage I (0–3.3 mm) – degeneration of hair cells, the outer hair cells first and then the inner hair cells, (immediately) followed by deterioration of the supporting cells. Other structures normal.

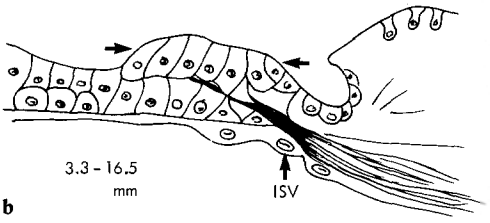


a



d

Fig. 4a and d. Almost all outer hair cells (*OHC*) are missing, arrow indicates intact OH-cell. Most inner hair cells (*IHC*) intact. Pilar cells (*P*) partially malformed



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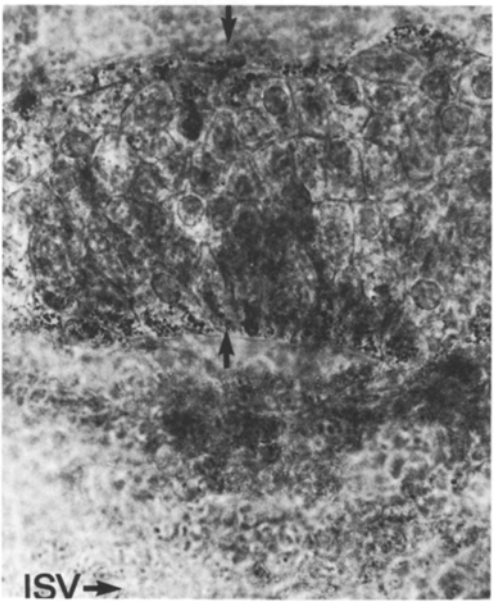
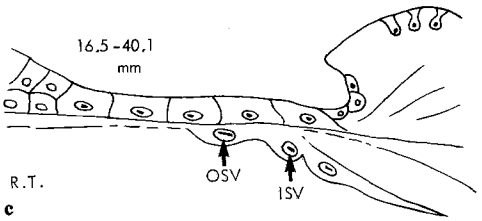


e

Fig. 4b and e. No normal hair cells left (area between arrows) Inner spiral vessel (*ISV*) visible

Fig. 4. Photographs (right) and reconstruction (left) of the three areas with different degrees of degeneration



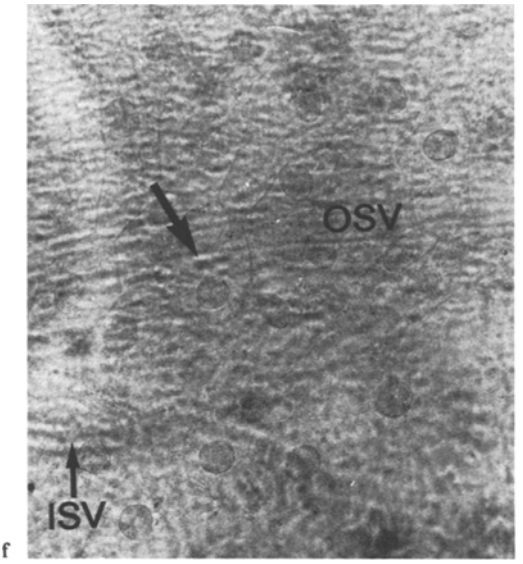


Fig. 4c and f. Spiral organ replaced by one layer of large, flat, polygonal cells (arrow). Both the outher spiral vessel (*OSV*) and the inner spiral vessel (*ISV*) can be seen

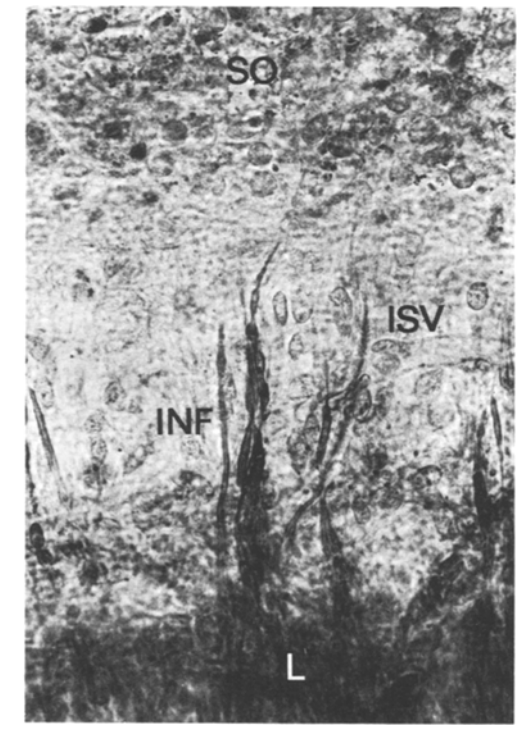


Fig. 5. Representative part of area between 16.5 and 21 mm *SO:* remnant of spiral organ. *ISV:* inner spiral vessel. *INF:* ingrowing nerve fibers. *L:* limbus (cp. Figs. 3a and 4b)

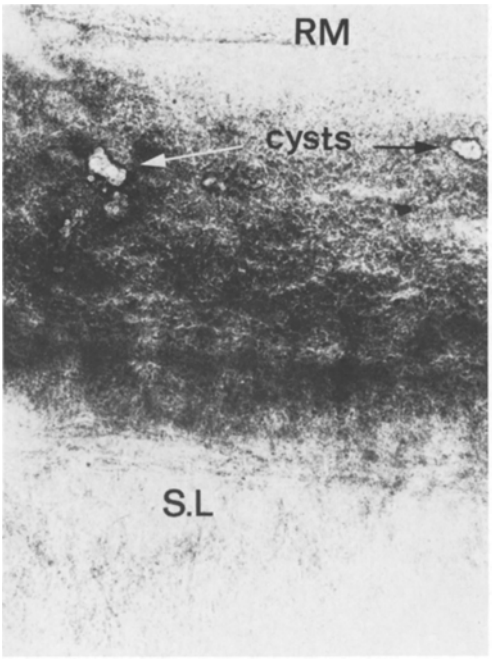


Fig. 6. Stria vascularis in the basal coil. *RM:* Reissner's membrane, *SL:* spiral ligament. Note the cysts

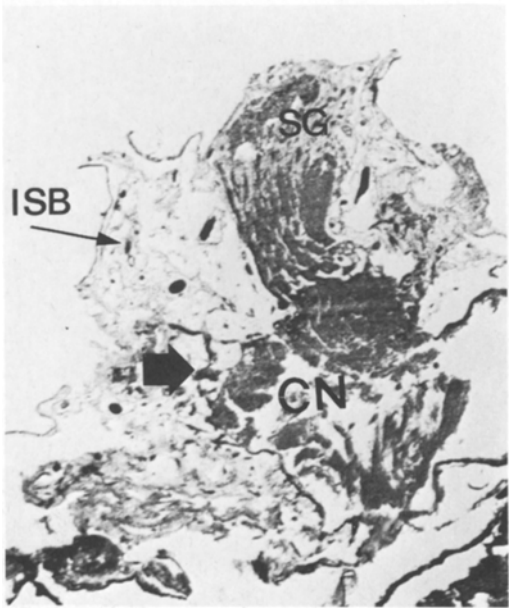


Fig. 7. Modiolus cross section. *SG:* spiral ganglion cells. *CN:* cochlear nerve. *arrow:* degenerated part of cochlear nerves. *ISB:* inner spiral bundle

Stage II (3.3–16.5 mm) – destruction of hair cells and supporting cells; height of sensory epithelium decreased; gradual secondary disappearance of nerve fibers and spiral ganglion cells. Ingrowth of new fibers in search of missing haircells. Vascular atrophy and formation of cysts in stria vascularis.

Stage III (beyond 16.5 mm) – spiral organ area replaced by a layer of large thin cells resting on the basilar membrane. Disappearance of all nerve fibers and ganglion cells. Complete devascularization of stria with formation of many cysts. Vascular anastomoses between scala tympani vessels and outer spiral vessel.

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