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# Usher Syndrome

## A Temporal Bone Report

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**T**he bilateral temporal bones of a deceased 84-year-old man who had been suffering from Usher syndrome were examined using light microscopy. Histopathologic examination disclosed degeneration of the organ of Corti that was most profound in the basal turn, degeneration of cochlear neurons in all of the turns, and severe loss of spiral ganglia in both cochleas. Endolymphatic hydrops of unknown cause and a functionally unimportant pit malformation in the macular utricle were observed in the right cochlea. We compared the aforementioned findings with temporal bone reports cited in the literature.

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Usher syndrome is characterized by bilateral congenital perceptive hearing loss or deafness with retinitis pigmentosa (RP) and has an autosomal recessive mode of inheritance. Hearing loss and RP are common in the general population, but rarely are found in combination.

In 1914, the ophthalmologist Usher<sup>1</sup> noticed the familial occurrence of the anomaly and believed that the symptoms were a specific genetic entity. Later studies established the autosomal recessive mode of inheritance.<sup>2-4</sup>

The prevalence of Usher syndrome in the general population is estimated to be 3 to 4.4 cases per 100 000 people.<sup>5-9</sup> This syndrome is the most frequent cause of combined deafness and blindness; it occurs in 0.2% to 7.9% of deaf people.<sup>10-13</sup>

The syndrome has different interfamilial grades of occurrence.<sup>5,14,15</sup> These findings have led to the syndrome being divided into at least two, and possibly four, subtypes.<sup>15-18</sup> So far, the most agreement has been reached about type I, characterized by RP with profound hearing loss and vestibular areflexia; and type II, characterized by RP, a moderately serious perceptive hearing loss (especially in the high frequencies), and a sensitive vestibulum.

Two other types are assumed to occur: type III, characterized by progressive hearing loss<sup>19-21</sup>; and type IV, which is rare, with the phenotype of type II characterized by X-linked recessive inheritance.<sup>22</sup>

These clinical variations have led to the assumption that the syndrome is caused by two or more genes located at different sites on the genome. This assumption was confirmed by recent gene-linkage studies; five loci are recognized for several types of Usher syndrome.<sup>23-29</sup>

Few histopathologic studies of Usher syndrome have been done. We report the findings of temporal bone examination in a deceased patient with type-I Usher syndrome and compare our findings with those cited in the literature.

### REPORT OF A CASE

The patient had been born deaf or had become deaf at a very young age. From age 24 to 28 years he was an inpatient at a psychiatric hospital because he was unmanageable at home. As a result of slow, progressive visual loss, he became blind at age 45 years.

From age 33 to 70 years, he lived in four different institutions for long-term care. He was then transferred to a deaf-blind institute for adults, where he remained until his death at the age of 84 years.

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The diagnosis of Usher syndrome was made by the consultant ophthalmologist at the deaf-blind institute. He found typical RP during a fundoscopic examination. At age 75 years, the patient underwent otologic examination performed by one of us (C.W.R.J.C.). Audiologic examination disclosed slight residual hearing in the right ear and serious down-sloping hearing loss in the left ear (**Figure 1**). In addition, a retraction pocket was observed in the right ear with an early-stage cholesteatoma that had caused partial erosion of the incudostapedial joint. No otoscopic abnormalities were found on the left side. Surgical intervention was not done, and vestibular examination was not performed.

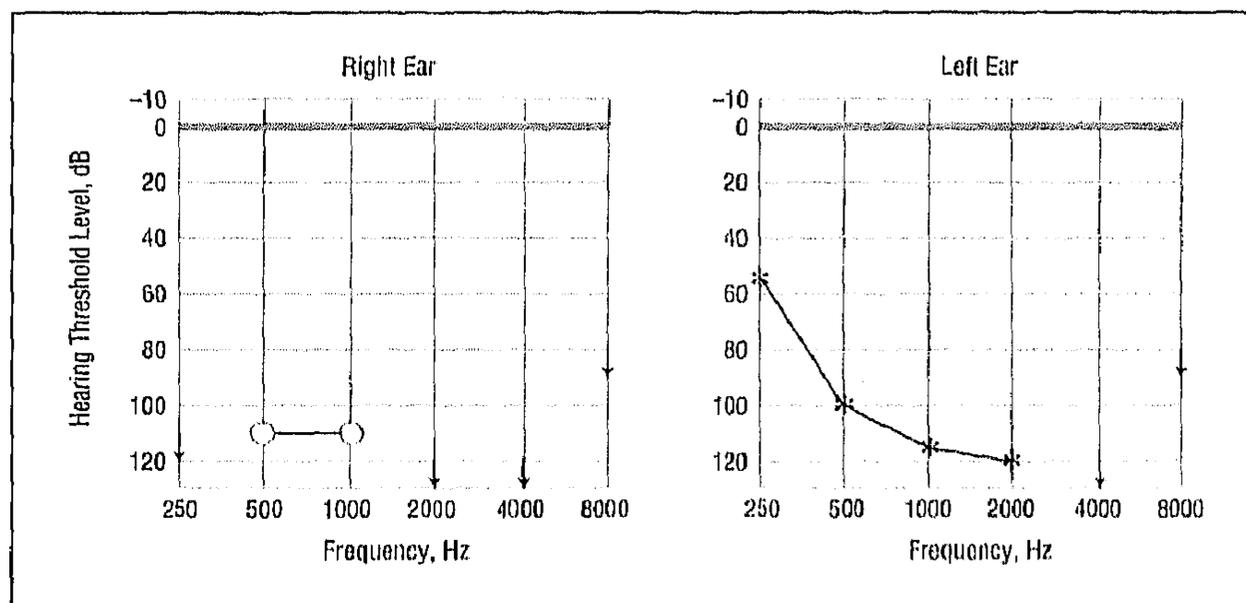
At age 84 years, the patient died of metastasized carcinoma, probably originating from the digestive tract. Examination of the family pedigree to the fifth generation excluded consanguinity between the patient's parents.

### HISTOPATHOLOGY

The temporal bones were removed in Nijmegen (the Netherlands) 3 hours postmortem, after injecting formalin into the middle ears through the tympanic membrane. Both temporal bones were sent to the Massachusetts Eye and Ear Infirmary, Boston, for histologic preparation and interpretation. Serial horizontal sections of both bones were prepared by previously reported standard methods.<sup>30</sup> Tissue sections showed good histologic preservation and preparation.

The spiral ganglia were graphically reconstructed by methods previously described.<sup>31,32</sup> The ganglion cell populations were determined for four segments of the cochlea (0 to 6 mm, 6 to 15 mm, 15 to 22 mm, and 22 to 32 mm) by multiplying each count by 0.9 to account for double counting of cells lying at the interface between sections and by 10 to account for cells located in unstained sections. The bony labyrinths were fully formed and the periosteal, endochondral, and endosteal layers seemed to be normal.

Both cochleas showed advanced atrophic changes in the organ of Corti (**Figure 2**). Through-



**Figure 1.** Audiogram of patient with Usher syndrome at the age of 75 years. Circle indicates air conduction in right ear; X indicates air conduction in left ear.

out most of the basal turn in each cochlea, the organ of Corti was missing. In the upper basal, middle, and apical turns, the organ of Corti consisted of mounds of cells in which Hensen's cells, atrophic and partly collapsed pillar and Deiters' cells, and inner phalangeal cells could be differentiated. In both cochleas, nuclei were located in the area that would normally contain inner hair cells, but it was unclear whether these were inner hair cells. They might have been border cells or inner phalangeal cells. Moderate to severe patchy atrophy of the stria vascularis was seen, but it was unclear whether this was worse than average for age (**Figure 3**, left). The tectorial membranes and limbus looked normal. The spiral ligament showed atrophic changes compatible with age. Reissner's membrane looked atrophic with decreased cellularity. On the right side, hydrops was present in all three turns; Reissner's membrane was distended into the midportion of the scala vestibuli (**Figure 2**, top left). On the left side, slight hydrops was present at the extreme apical end of the cochlear duct. This was not considered abnormal (**Figure 2**, top right).

The neuron counts were 11 268 for the right ear and 14 445 for the left ear (**Figure 4**). The cochlear neuron population was diminished more than would be expected as a function of aging (**Table 1**). The loss for the right and left ear was 40% and 23%, respectively, when compared with age-matched controls. Neuron losses were 68% (right ear) and 59% (left ear) compared with

normal neonates (**Table 1**). The spiral canals had a large central acellular area that extended through all the turns. The neuron populations congregated at the margins of this tubular acellular space.

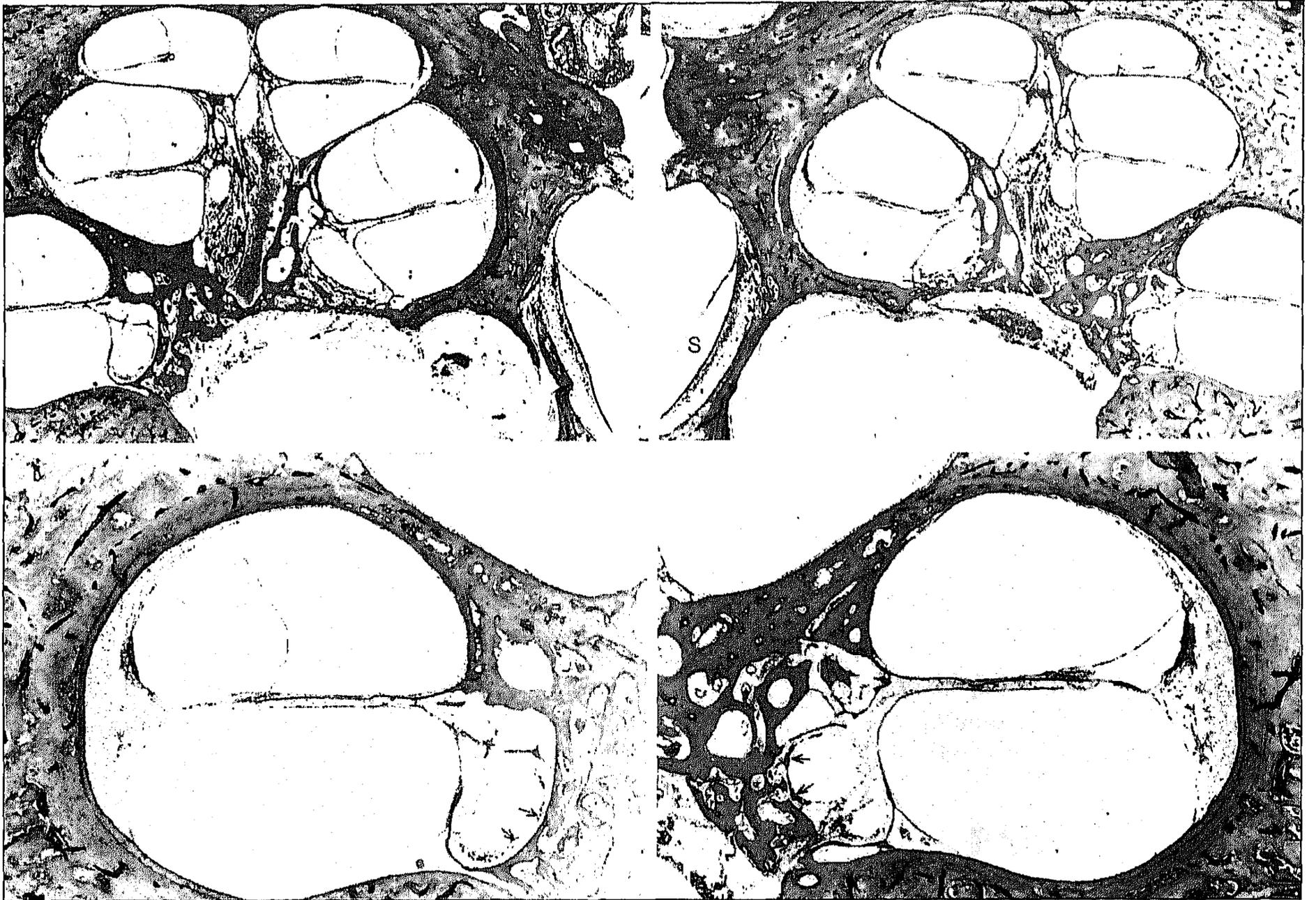
Both ears showed a loss of more dendritic nerve fibers than cochlear neuron cell bodies, which indicated that a retrograde neuronal degenerative process had occurred.

The saccular and utricular maculae and all the cristae of both ears looked normal. In the right ear, a small pit was seen in the utricular sensory epithelium at the posterosuperior part of the macula (**Figure 3**, right). This pit was partially filled with statoconia. This seemed to be an embryonic anomaly of no functional significance. Viewed in their area cribrosa, the superior and inferior divisions of the vestibular nerves looked normal in both ears; their trunks and the cochlear nerves were avulsed from the internal auditory canals. The facial nerve looked normal throughout the temporal bone.

The cochlear aqueduct was patent on the left side and obstructed with fibrous tissue on the right. This was considered functionally unimportant. The endolymphatic ducts were patent in both ears. The endolymphatic sacs had been avulsed from their foveate fossae during removal of the temporal bones.

### COMMENT

Since 1927, this is the second case report on type-I Usher syndrome that details the histologic findings in



**Figure 2.** Photomicrograph of the right (left, top and bottom) and left (right, top and bottom) ears of a patient with Usher syndrome. Both ears showed degeneration of the organ of Corti, loss of spiral ganglia cells and nerve fibers, and patchy degeneration of the stria vascularis. The right ear showed severe endolymphatic hydrops (original magnification  $\times 20$  [left, top and bottom],  $\times 40$  [right, top and bottom]). S indicates saccule.



**Figure 3.** Left, Higher magnification of the stria vascularis of the right ear with patchy degeneration. Right, Macular utricle of the right ear with a pit in the macular epithelium, partially filled with statoconia (original magnification  $\times 250$  [left],  $\times 170$  [right]).

temporal bones. Since 1906, 12 articles have been published about the temporal bone in 10 patients who were probably suffering from Usher syndrome.<sup>33-42</sup> In a few of these studies, it is doubtful whether the diagnosis of Usher syndrome should have been made because of the gaps in the clinical data. For example,

Alexander, quoted by Nager,<sup>34</sup> reported no objective audiologic findings, and Buch and Jorgensen<sup>35</sup> did not report RP. These two reports have been excluded from our comparison.

Because Usher syndrome is split into several genetic syndromes based on clinical features and gene-

linkage studies, it is likely that the pathologic abnormalities vary by type. The gaps in clinical data make it difficult to classify the patients (**Table 2**). In addition to vestibular function, the severity of the hearing loss is a major discriminating factor in the subclassification of Usher syndrome. Our patient's condition can be classified as type-I Usher syndrome because of his serious hearing loss and his vision symptoms. Admissions to psychiatric hospitals are also part of the syndrome.

The condition of the patients described by Siebenmann and Bing,<sup>33</sup> Cremers and Delleman,<sup>42</sup> and Nager<sup>34</sup> can be classified as type-I Usher syndrome based on the hearing loss. The two patients described by Nager<sup>34</sup> underwent vestibular testing, contrasted with the other patients and our patient, and the finding of vestibular hyporeflexia supports the diagnosis of type-I Usher syndrome. The condition of the patients described by Belal<sup>36</sup> and Shinkawa and

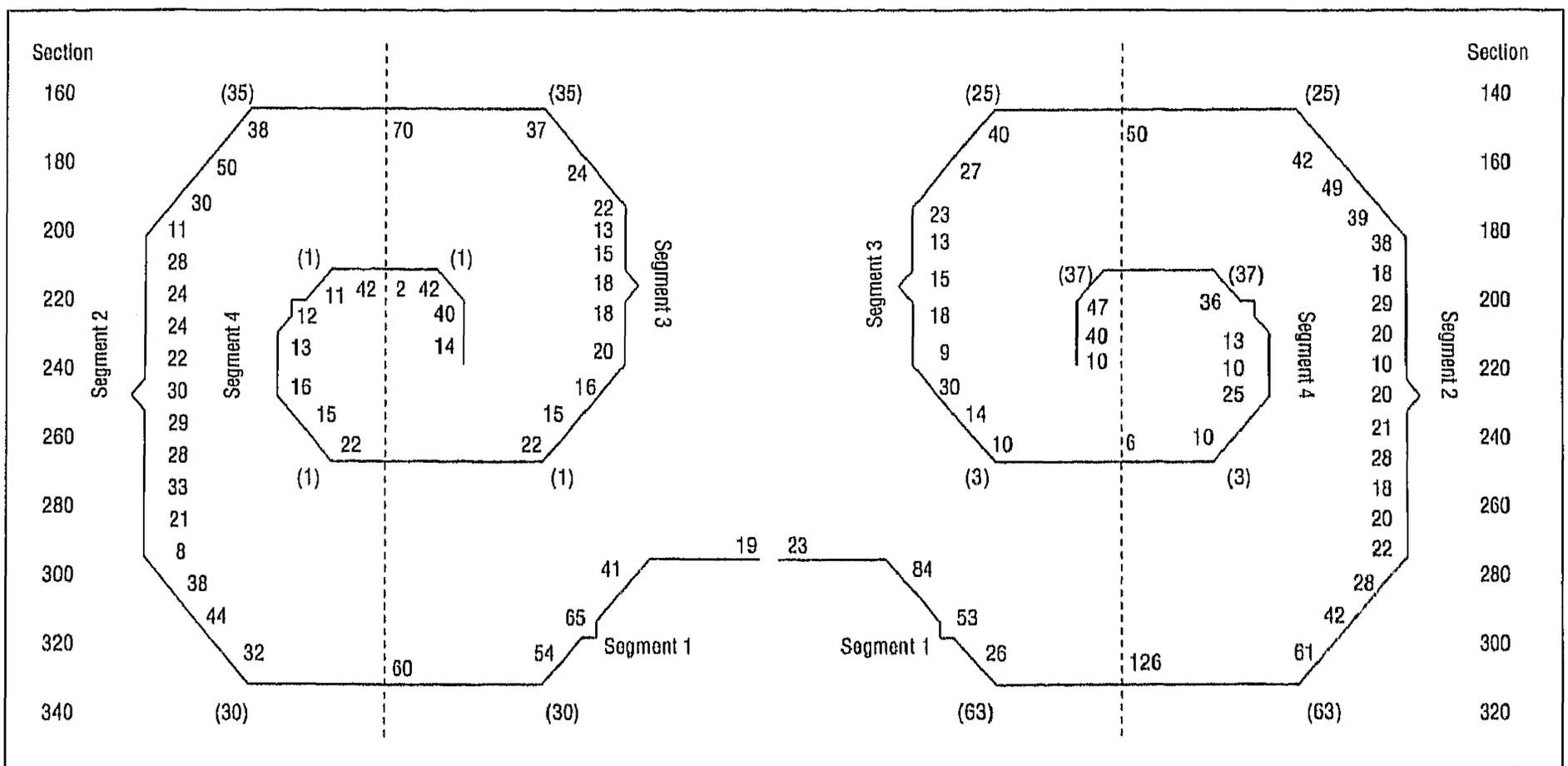


Figure 4. Left, Counts of spiral ganglion cells by segment in the right ear of a patient with Usher syndrome: 209 cells in segment 1; 557, segment 2; 256, segment 3; and 230, segment 4. Total (1252) was multiplied by 0.9 to account for double counting of cells lying at the interface between sections and by 10 to account for the cells located in the unstained sections, a total of 11 268 spiral ganglion cells. Right, Left ear: 249 cells in segment 1; 861, segment 2; 227, segment 3; and 268, segment 4; a total of 14 445 spiral ganglion cells (original magnification  $\times 1605 \times 0.9 \times 10$ ).

Table 1. Cochlear Neuron Counts in Patient With Usher Syndrome Compared With Age-Matched Controls and Normal Neonates

Neuron Count	Segment				Total
	1	2	3	4	
Age-matched controls	2250	7000	4775	4675	18 700
Patient					
Right ear	1881	5013	2304	2070	11 268
Loss, %	17	29	52	56	40
Left ear	2241	7749	2043	2412	14 445
Loss, %	1	1	57	48	23
Normal neonates	4900	13 400	8200	9000	35 500
Patient					
Right ear	1881	5013	2304	2070	11 268
Loss, %	62	63	72	77	68
Left ear	2240	7750	2040	2410	14 440
Loss, %	54	42	75	73	59

Nadol<sup>39</sup> (also described by Nadol<sup>40,41</sup> and Schuknecht<sup>37</sup>) should be classified as type III based on the progressive hearing loss. These three patients did not undergo vestibular examination.

The patient described by Schmidt<sup>38</sup> had a 30-dB hearing loss for low frequencies and no response above 1000 Hz and was probably a patient with type-II disease; data on progression of the hearing loss and vestibular findings are unavailable. Histopathologic data are not reported in detail in a few studies,<sup>37,38</sup> which makes it difficult to compare the study results.

The most important abnormali-

ties in our patient and in previous studies were degeneration of the organ of Corti, loss of cochlear neurons, and degeneration of the spiral ganglia. The severity of the abnormalities varied by study, but in all reports, degeneration of the organ of Corti was most distinct in the basal turns.

Atrophy of the stria vascularis, as found in our patient, was also mentioned in most studies cited in the literature,<sup>33,34,36,37,41,42</sup> but it was not found in the patient described by Shinkawa and Nadol.<sup>39</sup> Nager<sup>34</sup> reported that his two patients had abnormalities of the stria vascularis and atrophy of the spiral vessels, espe-

cially in the basal turn, and atrophy of the terminal vessels of the spiral prominence. Siebenmann and Bing<sup>33</sup> reported vascular degeneration of the cochlea and the vestibulum that was most prominent in the cochlea.

Vestibular abnormalities were not observed in all studies. Siebenmann and Bing<sup>33</sup> described a patient with vestibular hyporeflexia who showed partial degeneration of the macular epithelium and especially the crista epithelium without any clear abnormalities of the nucleus vestibularis.

In Nager's<sup>34</sup> first patient with vestibular hyporeflexia, utricular degeneration was found without nerve

**Table 2. Histologic Findings in Published Studies of Usher Syndrome\***

Author	Patient No./ Age, y/Sex	Type†	Cochlea			Vestibulum			
			Organ of Corti	Stria Vascularis	Spiral Ganglion	Sacculae	Utricule	Canals	Vestibular Neuron
Siebenmann and Bing <sup>33</sup>	1/69/M	<i>1</i>	D, in BT totally absent	D	D	D	D	D	D
Nager <sup>34</sup> (1927), reviewed by Buch and Jorgensen <sup>35</sup>	2/66/M	<i>1</i>	D in BT	D	D in BT	N	D	N	N
Nager <sup>34</sup>	3/20/M	<i>1</i>	D, particularly in BT	D, absent in BT	Severe D	N	N	N	N
Belal <sup>36</sup> (1975), reviewed by Shinkawa and Nadol <sup>39</sup>	4/38/M	<i>3</i>	D in BT	Scattered atrophy in BT	D in BT	D N <sup>39</sup>	D N <sup>39</sup>	D N <sup>39</sup>	N
Schuknecht <sup>37</sup>	5/38/M	<i>3</i>	D in BT	Patchy atrophy in BT	D in BT	?	?	?	?
Schmidt <sup>38</sup>	6/38/M	<i>2</i>	D partly missing in BT	?	?	?	?	?	?
Shinkawa and Nadol, <sup>39</sup> described by Nadol <sup>40,41</sup>	7/52/F	<i>3</i>	D in BT	N	D, severe in BT	N	N	N	N
Cremers and Delleman <sup>42</sup>	8/65/M	<i>1</i>	Severe D, partly missing in BT	A, patchy atrophy in BT	D, severe in BT	N	N	N	N
Present study	9/84/M	<i>1</i>	Severe D, missing throughout most BT	Moderate to severe patchy A	D	N	N (pit malformation in macula)	N	N

\*D indicates degeneration; BT, basal turn; N, normal; A, atrophy; ?, not mentioned.

†Numbers in italics indicate author's classification.

or vestibular involvement. In the patient described by Belal,<sup>36</sup> a decrease in sensory epithelium was noted in the macular utricle, sacculae, and three cristae. When his tissue sections were reviewed by Shinkawa and Nadol,<sup>39</sup> no vestibular abnormalities were found.

A normal vestibulum was also found in the patient with type III disease described by Shinkawa and Nadol.<sup>39</sup> In our patient with type I and the patient with type I described by Cremers and Delleman,<sup>42</sup> no vestibular abnormalities were found during light microscopic examination that could have explained the vestibular areflexia or hyporeflexia characteristic of type I. Vestibular examination results were unavailable for either patient to confirm this discrepancy. Vestibular findings were not mentioned in the studies by Schuknecht<sup>37</sup> and Schmidt.<sup>38</sup>

Our vestibular findings support the conclusion of Shinkawa and Nadol.<sup>39</sup> Based on their findings and reports in the literature, they did not believe that the pattern of cochlear and saccular degeneration (Scheibe's

deafness) proposed by Konigsmark and Gorlin<sup>43</sup> was associated with Usher syndrome.

Brain tissue was examined in few studies.<sup>33,34,42</sup> Cremers and Delleman<sup>42</sup> examined the brain and brain stem and found no abnormalities other than slight cortical atrophy. In contrast, analogue changes were found in the patients described by Siebenmann and Bing<sup>33</sup> and Nager<sup>34</sup>: severe atrophy of the primary acoustic center that extended into the peripheral cortex.

Many authors believe that the pathologic abnormalities in the cochlea are too slight for the severity of the hearing loss.<sup>33,34,36-38</sup> It was assumed initially that the abnormalities in the cortex and brain stem, which were considered to be secondary to the cochlear abnormalities, might possibly explain the hearing loss.<sup>33,34</sup>

Using electron microscopy techniques, Shinkawa and Nadol<sup>39</sup> and Nadol<sup>40,41</sup> suggested another cause. In the apical segment of the cochlea of a patient with type II who had no degeneration of the organ of Corti under light microscopy, there

seemed to be a significant decrease in the number of afferent nerve endings in the inner and outer hair cells.

In contrast, the histopathologic abnormalities in our patient corresponded with the severity of the hearing loss.

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