Histopathological and neuroradiological features of Usher syndrome type II

A. Ciorba*, A. Schrott-Fisher**, A. Berto*, R. Glueckert**, A. Janecke*** and A. Martini*

*Audiology Department, University Hospital of Ferrara, Ferrara, Italy; **Medizinische Universität Innsbruck, Universitäts-HNO Klinik, Labor für Innenohrlologie, Innsbruck, Austria; ***Medical University Innsbruck, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck, Austria

Key-words. Usher syndrome; cochlear findings; histopathology; neuroimaging

Abstract. Histopathological and neuroradiological features of Usher syndrome type II. Objective: To study the histopathological and neuroradiological features of Usher syndrome (USH), with particular focus on USH type II, an inherited disorder characterized by moderate to severe congenital hearing impairment and retinitis pigmentosa with onset in the late teens. Methodology: A report of four cases and literature review. Results and conclusion: Rare examples of histopathological and neuroradiological findings from four USH type II cases are presented. More studies like these are encouraged so that correlation studies between the morphological and clinical findings can be performed on the path to elucidate the pathogenesis of this heterogeneous disorder.

Introduction

Usher Syndrome (USH) is an inherited disorder characterized by retinitis pigmentosa and sensorineural hearing loss. Although the syndrome was first described by Albrecht Von Graefe in 1858, it was named after Charles Usher (1914), a British ophthalmologist, who presented a more exhaustive study of this disorder. His report of 69 cases of retinitis pigmentosa included 11 with profound hearing loss and 19 with partial hearing loss.1

The prevalence of USH is estimated to be between 1/16,000 and 1/50,000 based on studies in Scandinavia,2,3 the United Kingdom,4 and the United States.5 USH is reported to account for between 3% and 6% of the congenitally deaf population, about 18% of those with retinitis pigmentosa, and more than 50% of the deaf-blind population5,6 in developed countries.

USH is clinically heterogeneous. Three types are distinguished based on the degree of hearing loss, presence of vestibular symptoms, and severity of the retinitis pigmentosa. Several chromosomal loci have been assigned to the three clinical USH types.

The aim of the present study was to focus on the cochlear histopathological findings and neuroradiological aspects of USH type II, and to review the major genetic aspects of this syndrome.

Usher syndrome: focus on type II

Three USH types have been recognized so far: type I, in which the severe to profound hearing impairment is congenital with development of retinitis pigmentosa by the age of 10 years, and in which vestibular responses are absent; type II, in which there is moderate to severe congenital stable hearing loss with onset of retinitis pigmentosa in the late teens to early twenties, and normal vestibular responses; and type III, in which there is progressive hearing loss with a variable age of onset of retinitis pigmentosa.

To date, five genes and one locus for USH type I are known, three genes for USH type II are known, and one gene and one locus for USH type III are known (Table 1). Mutations in different USH genes can lead to a broad spectrum of phenotypes in the ear and eye, but recent reports provide evidence for the existence of an integrated Usher protein network in both the inner ear and the retina.6

The proteins encoded by the Usher genes (Table 1) are members of protein classes with different functions. Myosin VIIa is a motor protein; harmonin and SANS (scaffold protein containing ankyrin repeats and SAM domain) are scaffolding proteins; cadherin 23 and protocadherin 15 are cell adhesion molecules; and USH2A/usherin (isoform B) and VLG1b (very large G-coupled protein receptor 1 isoform B) are transmembrane proteins that could be involved in outside-in signalling. The protein encoded by
the gene associated with USH3A, clarin-1, is a member of the vertebrate-specific clarin family of four-transmembrane-domain proteins.6

Usher syndrome type II has at least three described subtypes, designated as types IIA, IIB, and IIC.

Particularly for Usher type II, at least three genes have been identified which seem to be involved in the pathogenetic process of the disease (Table 1). The USH2A gene codes for two alternatively spliced isoforms. The USH2A isoform is thought to be an extracellular matrix protein involved in protein-protein or protein-matrix interactions. Several analyses demonstrate USH2A expression in the basement membrane of several tissues in addition to the cochlea and the retina.7 The USH2B gene codes for the sodium bicarbonate co-transporter, NBC3. In the inner ear, NBC3 expression was detected in regions beneath the stria vascularis,7 as well as in the stereocilia, the lateral membrane, and in the synapses of the cochlear hair cells.7 An association of NBC3 with synapses was also described for the retinal neurons, in particular, for photoreceptor synapses.

Mutations in the very large G-coupled receptor 1b (VLGR1b) gene are responsible for USH2C. In the inner ear, VLGR1 expression is detected in the synaptic region and in the stereocilia of the sensory hair cells.7

Several USH type I genes have already been identified (Table 1). The myosin VIIa gene (MYO7A) was the first USH gene identified6 and at least half of the known USH type I cases are caused by mutations in MYO7A.6 To date, only a single gene has been

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### Table 1

<table>
<thead>
<tr>
<th>Locus Name</th>
<th>Location</th>
<th>Gene</th>
<th>Screening</th>
<th>Most Important Protein</th>
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<td>(14q32)</td>
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Histopathological and neuroradiological features of Usher syndrome type II identified in Usher syndrome type III; USH3A (clarin-1), a synaptic protein that is not expressed in photoreceptor synaptic terminals.

Cochlear histopathological findings of two Usher type II cases

Only 10 papers have been published so far concerning the histopathological features of the temporal bones of patients with USH, and the various reports are based on the same patient. In the current study, we present the histological data from two cases of Usher type II (Figures 1,2). Unfortunately, little anamnestic data are available. Case 1 is a male Usher type II patient who was affected by sensorineural hearing loss (audiogram not available) and retinitis pigmentosa. No vestibular symptoms have been described. Nevertheless, he was still able to see when he died at the age of 20 in a car accident. Case 2 is a male Usher type II patient affected with severe sensorineural hearing loss (audiogram not available), and retinitis pigmentosa. No vestibular symptoms had been reported. He died in adulthood.

The archival temporal bones were fixed with 4% formaldehyde.

![Figure 1](image_url)

Figure 1

Histopathological features of Usher syndrome type II. A. Celloidin embedded temporal bone from a patient with Usher syndrome. ST: scala tympani; SV: scala vestibuli. B. The spiral ganglion canal in the central modiolus seems to enclose normal densities of spiral ganglion neurons; from base (SG1) to apex (SG4). ST: scala tympani. C. The osseous spiral lamina (OSL) in the middle turn houses plenty of nerve fibers leading to the Rosenthalís canal with a normal density of spiral ganglion neurons (SG3), although the sensory organ on the basilar membrane (BM) has completely degenerated. D. The basilar membrane (BM) in the lower basal turn is void of any sensory epithelial cells. E. Detailed view of the osseous spiral lamina in the lower basal turn. Some nerve fibers (NF) persist. ST: scala tympani; SV: scala vestibuli.
Celloidin embedded temporal bone from a patient with Usher syndrome. A. The middle turn contains a normal density of spiral ganglion neurons (SG3) and peripheral processes traveling in the osseous spiral lamina (OSL). B. Sensory epithelium in the middle turn shows unimpaired morphology. BM: basilar membrane; OSL: osseous spiral lamina. C. Spiral canal in the upper basal turn. The few spiral ganglion neurons (SG2) only reveal central axons, while peripheral processes are missing. D. The organ of Corti has degenerated completely, and no nerve fibers persist in the osseous spiral lamina (OSL). BM: basilar membrane.

The cochlear histological findings of the presented cases are quite similar to each other. In both cases (Figures 1,2), the organ of Corti is completely degenerated. The spiral ganglion canal contains only few neurons at the base and more within the apical turns. The few spiral ganglion neurons at the base have only central axons with the peripheral processes missing; the osseous spiral lamina in the middle turn houses plenty of nerve fibres going to Rosenthal’s canal with a normal density of spiral ganglion neurons, although the organ of Corti on the basilar membrane (BM) is completely degenerated. Unfortunately, no data concerning the vestibule was available.

It has been reported that the histopathological features of the cochlea show a certain grade of uniformity, no matter what clinical type of USH is involved. In all the reported cases, a moderate to severe degeneration of the organ of Corti has been described which was most marked in the basal turn of the cochlea. Changes in the stria vascularis ranged from unde-
fined anomalies to hypoplasia or even atrophy. Spiral ganglion cells were said to be atrophied or decreased in number. Also the cochlear nerve fibres appeared to be diminished in number. Supporting cell elements of the organ of Corti have been reported to be diminished or degenerated. In the clinically more severe forms, atrophy of the stria vascularis, limbus, tectorial membrane, and Reissner’s membrane can also be present.1,10

The histopathological features of the vestibule described in the literature are more heterogeneous. USH type II and III are fairly homogeneous; in both cases, no vestibular abnormalities have been reported so far. These findings are not unexpected considering that USH type II and III are characterized by a functioning vestibule.10 Vestibular data in USH type I are more heterogeneous, and seem to vary from normal to severe degeneration of the epithelium of the utricles and saccules. This range of histological findings might be related to the differences in the genetic subtypes, or to different mutations within the same genetic subtype. Even similar gene mutations may lead to inter-individual histological differences based on their interaction with other genes.10

Neuroradiological features of two USH type II cases

Since only a few studies in the literature have described the CNS lesions present in USH patients, it is important to remark on this aspect. Magnetic resonance imaging (MRI) is the gold standard for addressing these features.11 We present the T1 weighted MRI images of two adult patients with USH type II (Figures 3,4).

Case 3 is a male USH type II patient with sensorineural HL that was diagnosed in his teens. An audiogram performed at age 36 years showed a moderate pan-totonal bilateral sensorineural HL, and he was diagnosed with retinitis pigmentosa at the age of 30 years. The MRI was performed when he was 47.

Case 4 is a male USH type II patient affected by sensorineural hearing loss since his teens. An audiogram showed a moderate...
bilateral sensorineural HL, gently sloping, and retinitis pigmentosa was diagnosed at the age of 11 years. The MRI scans were performed when he was 30 years of age.

Brain MRI was performed at the University Hospital of Ferrara after obtaining signed informed consent from the patients.

MRI scans of the brain were done with a 1.5 T unit with T1- and T2-weighted images in the axial, sagittal, and coronal planes using 3.0 to 5.0 mm thick slices. In both cases, a decreased volume of the cerebellum with an increased size of the subarachnoid spaces (especially the case of Figure 3) has been documented.

Concerning data from the literature, Bradley Schaefer G. et al., using MRI analysis in a group of 19 patients with USH types I and II, found a significant decrease in the intracranial volume and in the size of the brain and cerebellum with a trend toward an increase in the size of the subarachnoid spaces than in control subjects. They found that both USH type I and type II can involve the entire brain more or less equally. Analysing their imaging data, they also found that Usher syndrome type I patients are more severely affected, with more prominent atrophy and cerebellar involvement.

It is interesting to note that the clinical implication of these findings is that the inherent pathophysiologic process in Usher syndrome is not limited to the neurons of the optic and auditory nerves. In fact, the process appears to involve the CNS diffusely. Nevertheless, the fact that Usher syndrome patients tend to have a smaller intracranial vault with a smaller brain and cerebellum seems to indicate that the effects on the CNS are both of early origin and of long duration.

Conclusions

An overview of the recent molecular studies concerning USH type II pathogenesis is provided. Rare examples of histopathological and neuroradiological findings in cases of USH type II are offered. Particularly, the histological findings provide a phenotypical description of the USH type II phenotype of the inner ear. More studies like this should be encouraged in order to perform correlation studies between the morphological and clinical findings, on the path to elucidate the pathogenesis of this heterogeneous disorder.

References