Cochlear Histology in Alport Syndrome

Jai Shikotra MSc Audiological Science with Clinical Practice
Supervisor: Dan Jagger
email: jai.shikotra.23@ucl.ac.uk | d.jagger@ucl.ac.uk
UCL Ear Institute, University College London

Introduction

- Alport Syndrome is a rare hereditary genetic disease which affects the kidneys, ears and eyes, characterised by renal disease, hearing loss, and ocular abnormality (lenticonus), respectively.
- There are three modes of inheritance: X-linked (80-85% prevalence), Autosomal Recessive (10-15% prevalence), Autosomal Dominant (~≤5% prevalence)**[1]**.
- In Alport Syndrome, genetic mutation of the Type IV collagen results in malformation of the extra-cellular matrix, a component of basement membranes that bind sensory cells to connective tissue found in the kidney, ears and eyes, leading to the presenting symptoms**[2]**.
- Bilateral sensorineural hearing loss is a recognised symptom of Alport Syndrome**[1]** which manifests at adolescence, though onset differs between genders depending on mode of inheritance**[3]**.
- Hearing loss is progressive and can extend to profound levels**[4]**, though typically curtails at severe levels of hearing loss. Severity varies between genders, also dependent on mode of inheritance.
- Vestibular hypofunction has been associated with Alport Syndrome, though vertigo or dizziness is rarely experienced, going undiagnosed**[5]**.

Ethical Considerations

- The Ear Institute Temporal Bone Collection is licensed for storage, handling and study under the Human Tissue Act 2004 (#12161).

Aims of the Study

- To validate findings from existing studies, expand the knowledge base of pathologies associated with the disease and identify new pathologies not previous observed which may lead new avenues for therapeutic treatment to mitigate the progression of hearing loss in Alport Syndrome.

The Investigation

- Five human temporal bone samples, largely of young adults with Alport Syndrome were studied using light-microscopy.
- The samples were compared against approximately age-matched controls to identify areas of atrophy that may be attributed to the disease.
- Sites investigated (cochlear): organ of Corti, spiral ligament and stria vascularis, Reissner's membrane, spiral ganglion.
- Sites investigated (vestibule): vestibular end-organs i.e. semi-circular canal ampulla, Utricle and Saccule.

Key Findings

Cochlear abnormalities

- Four cases showed degeneration of the organ of Corti (fig. 1).
- The Reissner's membrane was partially or fully collapsed in all cases from the spiral limbus (fig. 1).
- Strial and spiral ligament atrophy observed in all cases (fig. 2).
- Depleted spiral ganglion cell numbers in three cases.
- Detachment of the basilar membrane from the organ of Corti and Claudius cells.

Vestibule abnormalities

- Collapsed membrane of the saccule wall in four cases (Fig. 3).
- Epithelial degeneration of crista ampullaris (lateral canal).

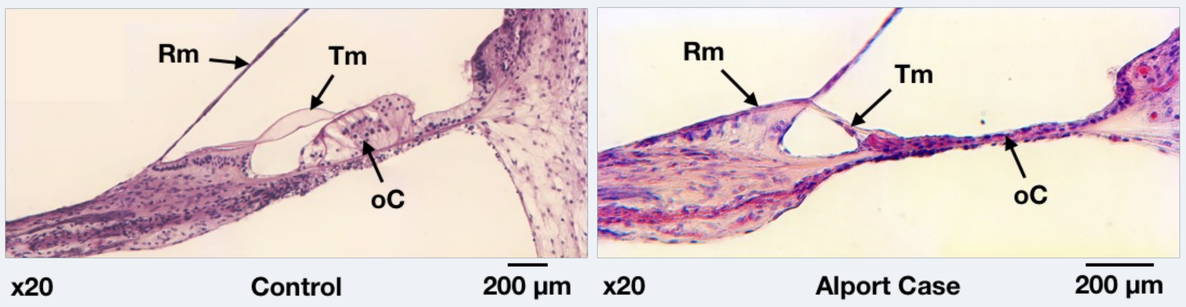

Fig. 1. Left image: Control with 'normal' organ of Corti (oC) and supporting cells. Right image: Alport case with absent or 'compressed' oC, flattened tectorial membrane (Tm) and collapsing Reissner's membrane (Rm).

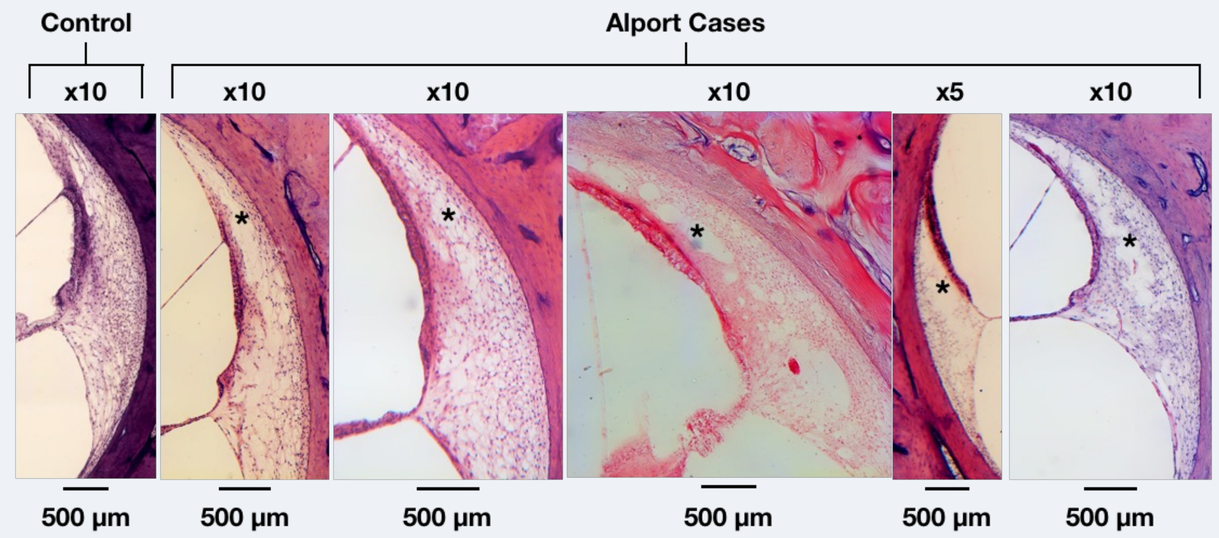

Fig. 2. The spiral ligament of the Alport cases presented patchy appearance of the fibrocytes (*) indicating a breakdown of the fibrocyte network. The stria also showed signs of thinning, possibly resulting from changes in the spiral ligament.

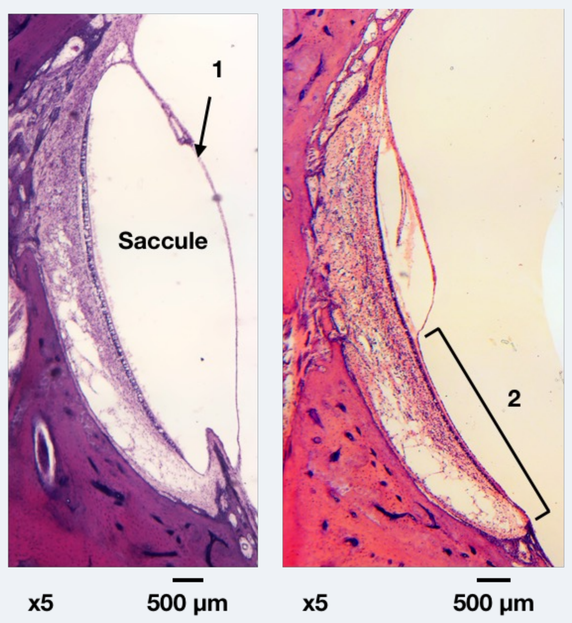

Fig. 3. Left image: Control sample showing 'normal' expanded vestibular membrane (1) of the saccule. Right image: Alport case showing the collapse of the vestibular membrane from the inferior region of the saccule (2).

Discussion

- How Alport Syndrome alters the micro-environment of the cochlea leading to hearing loss is still unknown.
- In the cochlea, Type IV collagen, COL4, has been found in the basement membrane adhering the basilar membrane and organ of Corti, amongst fibrocytes in the spiral ligament, the Reissner's membrane and spiral limbus**[6].**
- This study has demonstrated widely varying cochlear pathologies, in line with those reported previously**[7,8]**, which may contribute to hearing loss and can be linked back to localisation of COL4.
- Novel pathologies of vestibular organs have been also observed here, which may contribute to the reported vestibular hypofunction.

References & further reading: **[1]** C. M. Viveiros, L. D. Pereira and G. M. Kirsztajn, "Auditory Perception in Alport's Syndrome," Brazilian Journal of Otorhinolaryngology, vol. 72, no. 6, pp. 811-816, 2006; **[2]** F. R. A. Alves and F. d. A. Quintanilha Ribeiro, "Revision about hearing loss in the Alport's syndrome, analyzing the clinical, genetic and bio-molecular aspects," Brazilian Journal of Otorhinolaryngology, vol. 76, no. 6, pp. 813-819, November/December 2005. **[3]** C. Kashtan, "Alport Syndrome," 25 March 2024. [Online]. Available: https://rarediseases.org/rare-diseases/alport-syndrome/#complete-report. [Accessed 9 July 2024]. **[4]** S. N. Merchant, B. . J. Burgess, J. C. Adams, C. . E. Kashtan, M. . C. Gregory, P. A. Santi, R. Colvin, B. Collins and J. B. Nadol, Jr, "Temporal Bone Histopathology in Alport Syndrome," The Laryngoscope, vol. 114, pp. 1609-1618, Sept 2004. **[5]** S. Barozzi, D. Soi, E. Intieri, M. Giani, M. Aldè, E. Tonon, L. Signorini, A. Renieri, C. Fallerini, P. Perin, G. Montini and U. Ambrosetti, "Vestibular and audiological findings in the Alport syndrome," American Journal of Medical Genetics, vol. 182A, pp. 2345-2358, 2020. **[6]** A. F. Zehnder, J. C. Adams, P. A. Santi, A. G. Kristiansen, C. Wacharasindhu, S. Mann, R. Kalluri, M. C. Gregory, C. E. Kashtan and S. N. Merchant, "Distribution of Type IV Collagen in the Cochlea in Alport Syndrome," Archives of Otolaryngology Head & Neck Surgery, vol. 131, pp. 1007-1013, Nov 2005. **[7]** M. D. Crawfurd and P. J. Toghill, "Alport's Syndrome of Hereditary Nephritis and Deafness," Quarterly Journal of Medicine, vol. 148, pp. 563-576, Oct 1968. **[8]** G. J. Myers and H. R. Tyler, "The Etiology of Deafness in Alport's Syndrome," Archives of Otolaryngology - Head & Neck Surgery, vol. 96, pp. 333-340, 1972.
Useful websites: https://alportsyndrome.org; https://rarediseases.org/rare-diseases/alport-syndrome/#complete-report