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NF2-related schwannomatosis: A view from within the inner ear

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ABSTRACT

NF2-related schwannomatosis (NF2-SWN, formerly known as neurofibromatosis type 2) is an autosomal dominant disorder associated with the growth of bilateral schwannomas on the cochleo-vestibular nerves and meningiomas. NF2-SWN is caused by pathogenic variations in the *NF2, moesin-ezrin-radixin-like (MERLIN) tumour suppressor* gene. The mostly benign tumours can cause progressive sensorineural hearing loss, tinnitus and balance dysfunction. Outside the inner ear, tumours grow on other intra-cranial nerves, leading to further neurological issues and shortened life-expectancy. Here we re-evaluate some historic cases from our human temporal bone collection, and we review similar instances from the literature to highlight the structural and functional effects of such tumours on the cochlea and vestibular organs. Tumour growth is associated with the remodelling of sensory and ion-transporting epithelia, the loss of afferent neurons and hair cells, and signs of fluid dysregulation. These cases demonstrate the aggressive nature of this disease and the difficulties of surgically excising the bilateral tumours. They also emphasise the need for novel therapies that can slow or prevent tumour growth to preserve sensory function in people living with NF2-SWN.

1. Introduction

NF2-related schwannomatosis (NF2-SWN, formerly known as central neurofibromatosis, bilateral acoustic neurofibromatosis, and neurofibromatosis type 2) is an autosomal-dominant disorder with a birth incidence around 1 in 35,000 (Evans et al., 2010). It is caused by germline or mosaic heterozygous pathogenic variations in the *NF2, moesin-ezrin-radixin-like (MERLIN) tumour suppressor* gene (https://omim.org/entry/607379; formerly *NF2*) located on the long arm of chromosome 22 (Rouleau et al., 1987; Seizinger et al., 1986). This codes for Merlin, a cytoskeletal protein that contributes to the regulation of cell shape, growth and adhesion (Trofatter et al., 1993; Vlashi et al., 2024). Loss-of-function pathogenic variants in the gene are associated with dysregulation of Merlin-dependent signalling pathways (Laraba et al., 2023), causing the slow growth of tumours that underlie cochlear and vestibular deterioration, eventually resulting in hearing loss and imbalance (Dinh et al., 2020; Evans et al., 1992).

The majority of cases of NF2-SWN are associated with the growth of bilateral vestibular schwannomas (~90 %), benign tumours affecting the cochleo-vestibular nerves (Forde et al., 2021). Patients with NF2-SWN may have schwannomas on other intracranial, spinal and peripheral/cutaneous nerves that cause a range of compression symptoms (Ren et al., 2021). Meningiomas may also occur, affecting approximately ~50 % of those with NF2-SWN (Coy et al., 2020; Forde et al., 2021; Hexter et al., 2015). These develop in the layers of tissue that surround the brain and spine, and can produce headaches, seizures, or localised neurological symptoms. In addition, 30–50 % of people with NF2-SWN will develop ependymomas, usually intraspinal and most often located in the cervical spine (Coy et al., 2020).

It should be noted that 95 % of all vestibular schwannoma cases are unilateral and unrelated to NF2-SWN (Durham et al., 2023). Most of these cases occur sporadically, with a median age of 60 years at diagnosis. The age of onset for NF2-SWN is much younger, typically ranging from late teens to early adulthood for truncating mutations, though this can be as late as the fifth decade in mosaic cases (Halliday et al., 2017). The onset of hearing impairment in NF2-SWN sometimes precedes the clinical detection of vestibular schwannomas, suggesting that some auditory pathologies are independent of tumour burden (Asthagiri et al., 2012). The average life expectancy with truncating mutations that cause the most severe clinical signs and earlier hearing loss is approximately 46 years (Halliday et al., 2017). Poorer survival is associated with younger age at diagnosis and the presence of meningiomas (Forde et al., 2021; Halliday et al., 2017; Hexter et al., 2015).

The natural history of NF2-SWN from diagnosis to first therapeutic intervention, and subsequently managed disease course, has been described in detail for a large patient cohort (Forde et al., 2021). Current

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diagnosis of the disease incorporates genetic criteria to supplement clinical criteria (Plotkin et al., 2022).This recently revised approach helps to distinguish NF2-SWN from other forms of schwannomatosis (SWN) that have overlapping phenotypes (*SMARCB1*-related SWN and *LZTR1*- related SWN, see below). A diagnosis of NF2-SWN can be made when an individual has one of the following: (1) bilateral vestibular schwannomas, or (2) an identical *NF2* pathogenic variant in at least two anatomically distinct NF2-related tumours. Alternatively, they may have two major criteria (including (1) unilateral vestibular schwannomas, (2) a first-degree relative other than sibling with NF2-related SWN, (3) two or more meningiomas, or (4) an *NF2* pathogenic variant in an unaffected tissue such as blood), or one major and two minor criteria (including more than one ependymoma, meningioma or schwannoma, or disease-specific ocular phenotypes).

NF2-SWN bears some similarities to neurofibromatosis type 1 (NF1, formerly known as peripheral neurofibromatosis), a genetically distinct condition that features tumours on or under the skin (neurofibromas) and pigmented café au lait spots on the skin, but does not have a link to vestibular schwannomas (Kresak and Walsh, 2016). NF1-associated neurofibromas may develop on peripheral nerves, sometimes leading to pain and numbness. These commonalities led to the "neurofibromatoses" often being considered as branches of the same disease. This inter-woven history has been documented by others (Ahn et al., 1996; Plotkin et al., 2022; Ruggieri et al., 2017; Tamura et al., 2024). In Section 2 we provide a more focused history of NF2-SWN alone. Although genetically distinct, NF2-SWN shares phenotypic similarities with other forms of SWN, including those arising from pathogenic variants of the *SMARCB1* or *LZTR1* genes that are also located on chromosome 22 (Coy et al., 2020; Kresak and Walsh, 2016; Plotkin et al., 2022). LZTR1-related SWN and SMARCB1-related SWN are also characterised by the development of multiple peripheral nerve schwannomas (Kresak and Walsh, 2016). In common with a minority of NF2-SWN cases, unilateral vestibular schwannomas can be a feature of LZTR1-related SWN (Smith et al., 2012), though vestibular schwannomas are not associated with SMARCB1-related SWN.

A number of recent works can provide the reader with more details on the underlying genetics and patterns of inheritance of NF2-SWN, the cellular signalling pathways implicated, and recent clinical trials and treatments available for those living with this disease (Coy et al., 2020; Franco-Caspuenas et al., 2025; Ghalavand et al., 2023; Laraba et al., 2023; Plotkin et al., 2022; Ren et al., 2021; Ruiz-Garcia et al., 2024; Vlashi et al., 2024). The focus of this review, though, is how bilateral vestibular schwannomas affect the tissues of the human inner ear. To help demonstrate this we have re-evaluated historic cases within our temporal bone collection at the UCL Ear Institute (see Section 2). These case studies from early in the 20th Century have been presented previously in the literature with detailed description of the patients' symptoms (de Klejn and Gray, 1932; Gray, 1933), though they have been largely ignored in more recent times. Although not genetically confirmed, histology paired with the available clinical details allow these cases to be diagnosed retrospectively as NF2-SWN. As outlined above, the disease can be diagnosed solely by the presence of bilateral vestibular schwannomas without other necessary criteria (Plotkin et al., 2022), and all three cases meet that description. The temporal bones demonstrate migration patterns of tumours within the inner ear (and beyond), but they also highlight direct and indirect consequences of tumour growth on specific tissue types. Importantly, these cases exemplify the relentless nature of this disease, and the need for early diagnosis and treatment to prevent or slow irreversible changes to hearing and balance functions.

2. A (brief) history of NF2-SWN and the inner ear

NF2-SWN was first described in 1822 by John H. Wishart, a Scottish surgeon and President of the Royal College of Surgeons in Edinburgh (Wishart, 1822). The patient, a 21-year-old male, came to Wishart's attention in 1818 "*on account of a deafness affecting both ears, which had been coming on gradually for several weeks*". Wishart saw the decline in the young man's hearing and sight between visits, and the development of muscle spasms. This led Wishart to make an incision into a tumour on the patient's head to ascertain its nature: "*On examination, we found that there was a small opening in the cranium, and that the tumour protruded through it, covered by the dura mater. A very small puncture was made in the investing membrane with an eye-instrument, but no discharge took place.*" The patient died just two weeks later, possibly as a result of an infection at the incision site. During post-mortem dissection, Wishart noted the presence of numerous tumours that arose from the dura mater (identifying them most likely as meningiomas) and from the cranial nerves. Most notable, was "*a tumour the size of a small nut, and very hard*", that was attached to each the 8th cranial pair of nerves "*just where they enter the meatus auditorius internus*", thus identifying them as bilateral vestibular schwannomas (Ahn et al., 1996). This early-onset and aggressive presentation of NF2-SWN involving concurrent intracranial schwannomas and meningiomas is still referred to as the "Wishart" type. Cases that present later in life with slower growing tumours are termed the "Gardner" type after its initial description ~100 years later (Gardner and Frazier, 1930).

In 1882 Friedrich von Recklinghausen provided a comprehensive report on the condition that would later be known as NF1 (Kresak and Walsh, 2016). During a large part of the 20th Century, a number of cases of what would now be diagnosed as NF2-SWN were included within the catch-all description of "von Recklinghausen's disease" (Ahn et al., 1996; Plotkin et al., 2022; Ruggieri et al., 2017; Tamura et al., 2024). One reason for this delayed distinction was an incorrect assertion of the eminent neurosurgeon Harvey Cushing, that bilateral vestibular schwannomas were a feature of von Recklinghausen's disease (Ruggieri et al., 2017). A series of studies in the 1930s began to consider the heritability of "*central neurofibromatosis*" and the nature of intracranial tumours seen in these cases. Gardner and Frazier studied a large family in which many members over a number of generations had bilateral hearing loss plus other symptoms (Gardner and Frazier, 1930). They proposed a dominant Mendelian inheritance of "*acoustic neurofibromas*" that affected the 8th cranial nerves bilaterally, and that the tumours originated on the vestibular portion of those nerves. Further microscopy studies around this period began to provide new descriptions of the growth patterns and histological features of bilateral vestibular schwannomas, and detailed their effects on the sensory and non-sensory tissues of the inner ear (de Klejn and Gray, 1932; Gray, 1933; Scott, 1938). Studies of NF2-SWN temporal bones have appeared only periodically in the otology literature since then (see Section 4).

3. Human temporal bone studies of bilateral vestibular schwannomas: the London experience

3.1. Building a temporal bone collection at University College London - a 100-year project

The UCL Ear Institute houses a repository of temporal bones, formed by merging separate collections from sites across London. The oldest cases from the 1920s onwards were collected at the Ferens Institute of Oto-Laryngology at Middlesex Hospital and at the National Hospital Queen Square by the pioneering otologist Charles Skinner Hallpike (1900–1979). These were added to those collected more recently at The Institute of Laryngology and Otology by Imrich Friedmann (1907–2002) and Leslie Michaels (1925–2018). Surviving records associated with the collection show that samples were prepared in keeping with standard methods described elsewhere (Schuknecht, 1993), using formalin-based fixatives, and celloidin for embedding and hardening. As such, the samples are subject to typical artefacts such as tissue shrinkage. Temporal bone sections are typically cut at 20 μm thickness in the horizontal plane using a microtome, resulting in 400–500 sections per sample, of which every tenth sample is kept for staining and inspection. The current

collection is held under a licence granted by the UK Human Tissue Authority (#12161) for storage and anatomical study.

The collection mostly contains cases of otological interest, including unilateral and bilateral vestibular schwannomas, otosclerosis, Ménière's disease, and damage to the inner ear caused by infections or ototoxic drugs. As such, there are very few otologically "normal" cases that can provide age-matched controls, particularly from the earliest period covered by the collection. In Fig. 1 we detail a case from the mid-1950s of an 18-year-old female who was examined clinically due to headaches and nystagmus. Hearing and balance tests carried out one year before her death suggested normal inner ear function. The post-mortem revealed a significant hydrocephalus in the left hemisphere. The records do not detail the delay between death and fixation and preparation of the temporal bones, but they do reveal that typical of this period they were fixed using Witmaack's solution (formalin-based). Examination of the samples at the time recorded no otological abnormalities. To our knowledge, these findings were not reported in the literature. A low magnification image (Fig. 1A) presents a summary view of the inner ear, highlighting the afferent innervation of the cochlea and vestibular maculae. More detailed examination of the cochlear tissues demonstrates typical presentations of the organ of Corti, Reissner's membrane, stria vascularis and spiral ganglion (Fig. 1B-E). Closer inspection of the saccule shows the entry route for the nerve fibres and the positions of the sensory epithelium and the endolymphatic space (Fig. 1F).

Within the Ear Institute's collection are cases that would meet the current diagnostic criteria for NF2-SWN, specifically that they feature bilateral vestibular schwannomas. Although these haven't been genetically confirmed, they do show key pathological features in common with

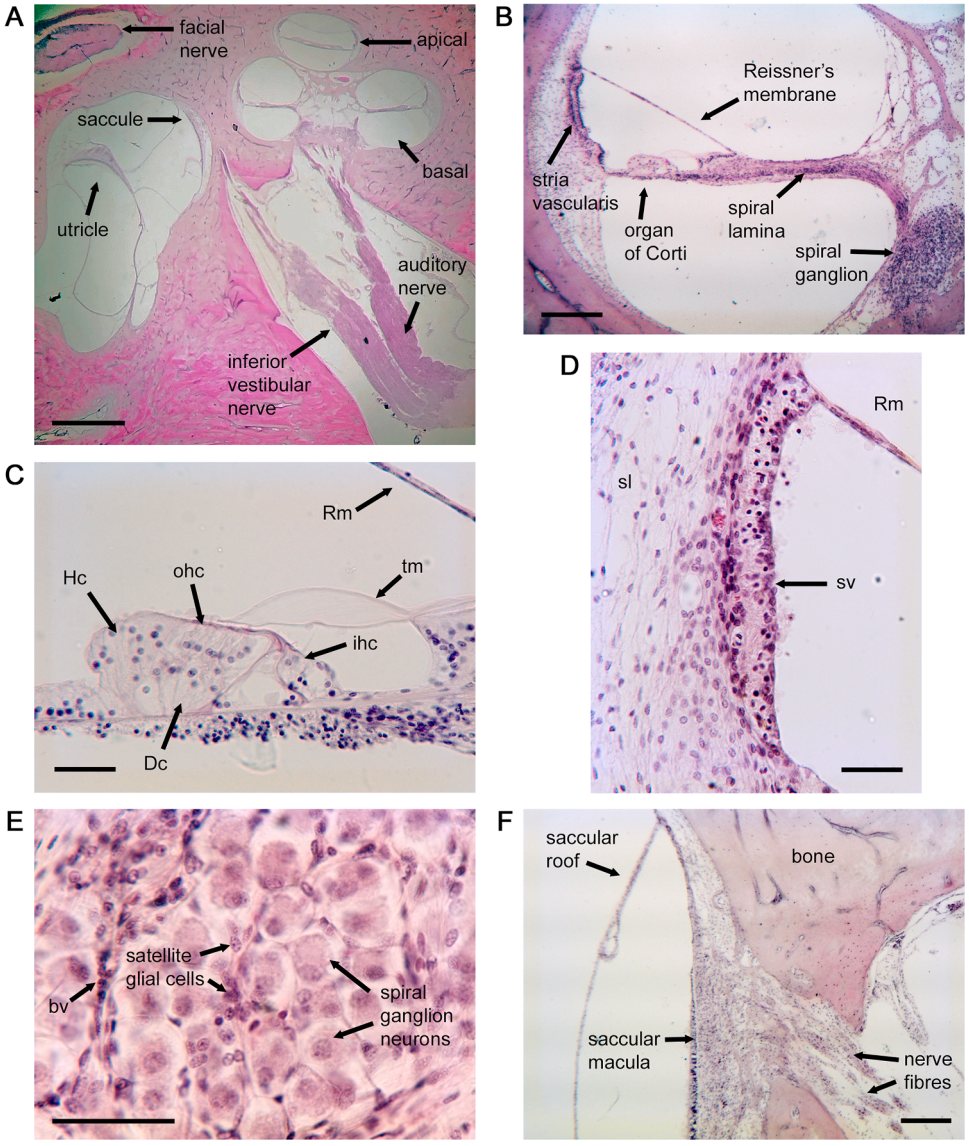

Fig. 1. The left inner ear of an 18-year-old female without gross otological pathologies.
A, Low-power cross-sectional view of the cochlea, saccule and utricle, indicating the normal positions of the inferior vestibular nerve and auditory nerve. **B**, View of the mid-basal cochlear region. **C**, Detail of the organ of Corti, showing the outer hair cells (ohc) and inner hair cells (ihc), their supporting cells (Deiters' cells, Dc; Hensen's cells, Hc), and Reissner's membrane (Rm) and the tectorial membrane (tm). **D**, The cochlear lateral wall, showing the relationships between stria vascularis (sv), the spiral ligament (sl) and Reissner's membrane (Rm). **E**, The spiral ganglion houses the cell bodies of the spiral ganglion neurons and their attendant glial cells. The course of a blood vessel (bv) is marked. Some neurons display a modest amount of post-mortem shrinkage, but there are no large spaces suggesting neuronal numbers are normal. **F**, Detail of the saccule, showing the position of the sensory epithelium (saccular macula) and the entry point of nerve fibres. The saccular roof membrane divides the endolymphatic space adjacent to the macula from the perilymphatic space of the vestibule. UCL case F265; haematoxylin and eosin staining. Scale bars: **A**, 2 mm; **B** & **F**, 100 μm; **C-E**, 50 μm.

other cases of NF2-SWN described elsewhere (see Section 4). The earliest of these include samples studied by Albert Alexander Gray (1868–1936; Fig. 2). Gray was originally from Glasgow, where he studied medicine (Obituary, 1936). He commenced his early otolaryngologic training in Leipzig and Munich, and returned to Scotland in 1898, where he became Surgeon on Diseases of the Ear at the Western Infirmary, Glasgow, and Lecturer in Diseases of the Ear at the University. There, he developed techniques to prepare the labyrinth by dissolving the bony capsule. This technique was then extended to the preparation of the cochlea, which allowed him to preserve microscopic sections for analysis (Gray, 1903). Soon after he published other works, most notably two volumes of '*The Labyrinth of Animals*' (Gray, 1907–1908), which presented stereoscopic images of the inner ear of mammals, birds, reptiles and amphibians sourced largely from the Zoological Society of London. His research into the underlying mechanisms of otosclerosis and the development of treatments for this condition were described in several publications including an influential book (Gray, 1917). He was Gold Medallist of the American Academy of Ophthalmology and Otology in 1911 and served as President of the Section of Otology of the Royal Society of Medicine from 1914 to 1916. In 1927 Gray became the librarian and curator of the Ferens Institute, positions he held until his death, while on holiday in Scotland in 1936. "Albie" Gray published two notable papers that focused on three patients found to have bilateral "*acusticus tumours*" (schwannomas) and diagnosed with "*von Recklinghausen's disease, the central type*" (de Klejn and Gray, 1932; Gray, 1933). Three temporal bones from two of these patients are held within the UCL Ear Institute collection, and we have reviewed and re-imaged these as exemplar cases of how NF2-SWN affects the inner ear.

3.2. Insights into NF2-SWN and the ear: a case study of a young male

The first of Gray's studies reports a male (UCL case F15, detailed here in Figs. 3–6) who was 40 years old at the time of his death (de Klejn and Gray, 1932). The patient was first met by Gray's clinical colleague Adrian de Klejn in 1917 aged 28, and at that time he was experiencing cerebral disturbances associated with slight muscle weakness and difficulties in walking. In 1919 the patient was reported as "*quite deaf in the left ear*" and had a "*partial deafness due to labyrinthine disease*" in his right ear. Numerous tumours in the skin on the back and of the right arm were described. He experienced a horizontal nystagmus when looking to the left and to the right. Following tuning fork hearing tests and balance testing it was deduced that there was a "*considerable degree of nerve deafness*" in the right ear. X-ray examination revealed erosion of the internal auditory meatus on both sides, and only a year later (1920) this was noted to be more striking. At that time, the patient could hear a conversational voice only at a distance of one inch from the right ear. There was no response to vestibular tests in either ear. Over three years later, on his third examination, the patient was "*quite deaf in both ears*", with again no response to vestibular tests in either ear. There were no compensatory eye movements on either side, and he was almost completely blind. The patient died in 1929, aged 40. Although the cause of death was not directly identified, a post-mortem examination stated there was "*typical Recklinghausen's disease of the brain*", though the phenotype (including bilateral schwannomas as described below) would meet the current diagnosis of NF2-SWN.

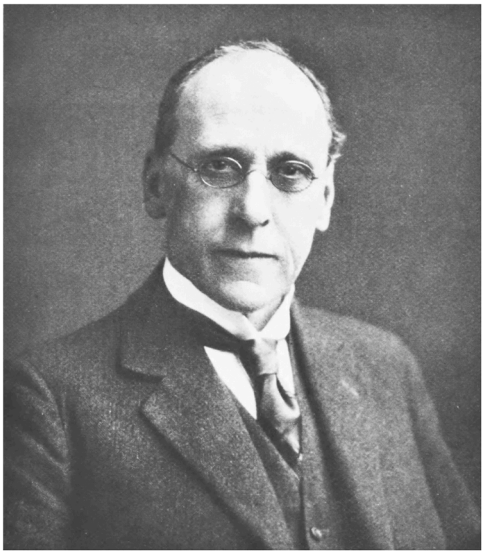

Fig. 2. Albert A. Gray (1868–1936), librarian and curator of the Ferens Institute of Oto-Laryngology at the Middlesex Hospital in London. Despite his somewhat austere appearance, a colleague (Cleminson, 1936) reflected: "*Unconsciously he cast the charm of his rare nature over everyone who came into contact with him and to know Gray was to love him. It can be said of few men in the full sense in which it can be said of him that he was a man without enemies and without enmity. He never showed resentment or jealousy and indeed seemed to live in a serene and peaceful land of his own where the common faults of human nature dared not intrude.*".

The pathological report showed that the posterior surface of the petrous portion of the right temporal bone was eroded and replaced by a tumour as far forward as the carotid canal. The wall of the internal auditory canal was "*completely destroyed*", with "*no trace of the seventh and eighth nerves*". The tumour had grown along the horizontal portion of the facial canal, destroying the facial nerve. Within the cochlea, the tumour had advanced through to the modiolus (Fig. 3A; equivalent to Fig. 5 in de Klejn & Gray's original study). In the middle turn, a net-like collection of tumour cells had spread from the modiolar wall into scala tympani (marked * in Fig. 3B). Reissner's membrane was in "*its normal position throughout the whole of its course*" (Fig. 3A-D). Stria vascularis had undergone vacuolization, with "*the cells that normally line the surface having entirely disappeared*" (Fig. 3C,D). The spiral ganglion had been destroyed by the tumour tissue that had taken its space in the modiolus (Fig. 3E; equivalent to original Fig. 10 in de Klejn and Gray, 1932). In the upper basal region, the outer hair cells were largely absent, and the supporting cells had expanded to fill spaces the hair cells had left behind (Fig. 3F). This formation is consistent with a repair process mediated by the supporting cells before death (Taylor et al., 2012), rather than the hair cells being lost due to post-mortem autolysis. The epithelium in the lower part of the basal turn had almost disappeared (Fig. 3G; equivalent to Fig. 9). In this region there were no hair cells, Hensen's cells, Deiters' cells or other recognisable supporting cell types. A non-specialised epithelium of squamous cells spanned the space between the inner sulcus and the outer sulcus. Perhaps reflecting this apparent base-to-apex progressive degeneration, the original study noted "*if that patient had lived longer, the upper part* (i.e. the organ of Corti in the middle and apical turns of the cochlea) *might also have disappeared*".

Deeper serial sections revealed the vestibule had been invaded by a schwannoma (Fig. 4). This formed as a multi-lobulated oval mass in the region of the saccule (Fig. 4A; equivalent to original Figure 4). The saccular macula had been pushed into the vestibule by the tumour, but as the original study noted "*the neuro-epithelial cells of the macula sacculi are in no way destroyed, and preserve an unbroken surface in spite of the fact that they have been pushed so far forwards into the cavity of the saccule.*" The tumour did not contact the stapes. The original position of the utricular macula was occupied by a large schwannoma (Fig. 4B), and this spread into the region of the adjacent crista ampullaris of the lateral semicircular canal. The sensory epithelium of the superior crista ampullaris was replaced by a schwannoma (not shown). Sections containing the posterior crista were not available for study.

The haematoxylin and eosin staining (H&E; for nuclei and cytoplasm, respectively) within the internal auditory canal where the cochleo-vestibular nerve would normally lie revealed characteristic pathological signatures typical of NF2-SWN (Fig. 5). The neoplasms mostly had the appearance of a schwannoma (Fig. 5A,B), but nearby there were also growths that carried the hallmarks of meningiomas

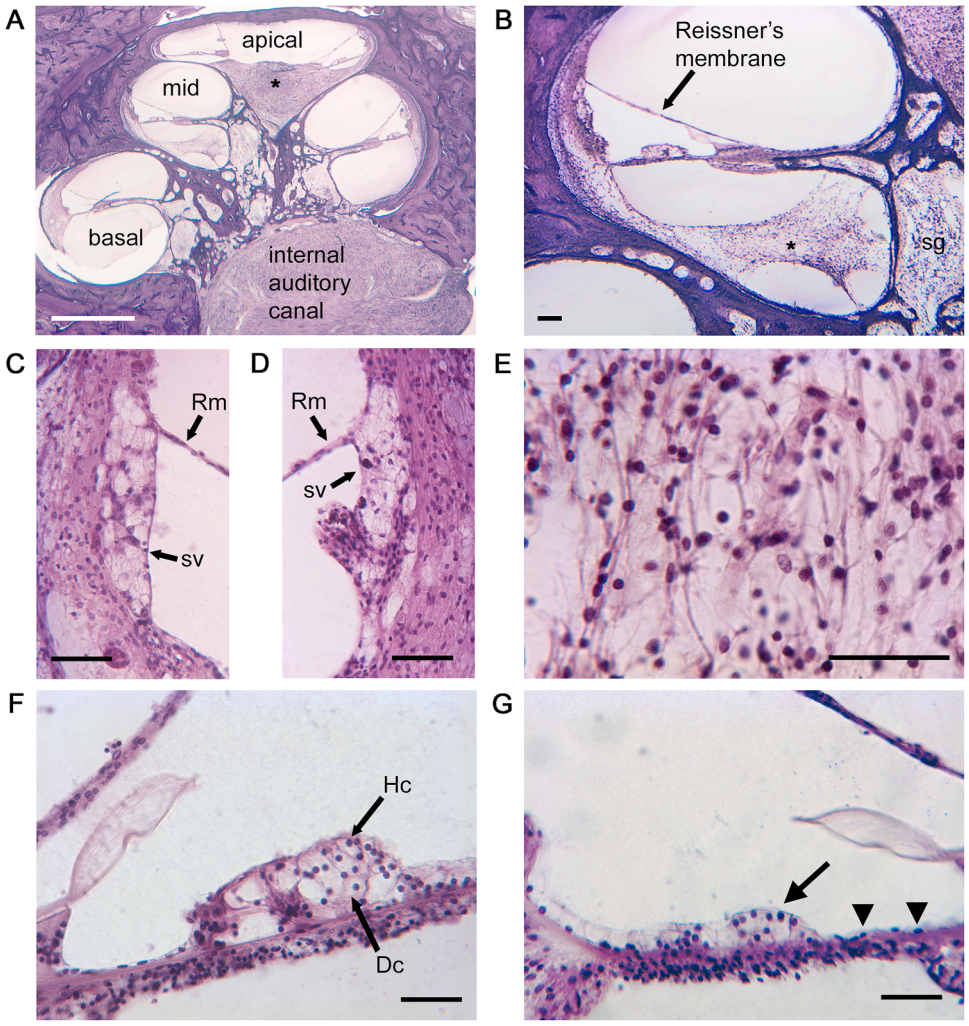

Fig. 3. The right cochlea of a 40-year-old male with NF2-SWN.
A, A large schwannoma occupies the internal auditory canal, and another fills Rosenthal's canal in the apical cochlear region (marked *). **B,** A view of the mid-turn region shows the positions of the spiral ganglion (sg) and Reissner's membrane. A net of tumour cells (*) is stretched across scala tympani. **C-D**, The cochlear lateral wall in the mid-basal region, showing vacuolisation of stria vascularis (sv). **E**, In the spiral ganglion there is no evidence of neuronal cell bodies, the spaces they normally occupy are filled by fibrous cells. **F,** The organ of Corti in the upper basal region is missing identifiable outer hair cells, but Deiters' cells (Dc) and Hensen's cells (Hc) can be identified. **G,** The sensory epithelium in the most basal region is without recognisable supporting cell types (large arrow). There are flattened squamous cells (arrowheads) on the upper surface of medial portion of the basilar membrane stretching towards the inner sulcus. UCL case F15; haematoxylin and eosin staining. Scale bars: **A**, 1 mm; **B**, 100 μm; **C-G**, 50 μm.

(Fig. 5A,C). The schwannomas were generally dominated by dense cellular areas (so-called Antoni type A regions), but in some areas there were relatively larger areas of cytoplasm (Antoni type B regions), and often the cigar-shaped nuclei formed palisaded layers typical of Verocay bodies (Fig. 5B). In comparison, the cells within the meningiomas had more regular and circular nuclei that were densely packed (Fig. 5C), and these areas appeared to be highly vascularised. There were often groups of psammoma bodies of varying sizes close to the schwannomas or meningiomas, particularly where the tumours lay adjacent to bone (Fig. 5D). These concentric lamellated structures are commonly seen in or close to 8th nerve schwannomas or meningiomas (see Section 4.1).

The *left* temporal bone from this case was more widely affected by tumours (Fig. 6A-D). A schwannoma extended throughout the cochlea from the direction of the internal auditory canal, removing all traces of the cochlear lateral wall, the organ of Corti and all neural structures (Fig. 6A). The walls of the internal auditory canal were "*completely destroyed*". In these serial sections there was evidence of heavily-stained new bone growth in the cochlea where the sensory tissues had once been (marked * in Fig. 6A). Gray noted that this bone contained "*a considerable number of spaces which are filled by bone marrow*". Closer inspection of the schwannoma within the basal region of the cochlea revealed Antoni type A and B regions of cells, and Verocay bodies (Fig. 6B). In deeper sections, the schwannoma had completely filled the vestibule and was pushing against the inner face of the stapes footplate (Fig. 6C; equivalent to original Fig. 14). The schwannoma had escaped through the round window into the middle ear (Fig. 6D; equivalent to original Fig. 13), and deep into the semi-circular canals.

In summary, the right ear represents the early effects of the aggressive form of the disease on inner ear tissues (Figs. 3–5). A combination of schwannoma and meningioma growths were in close association, and schwannoma tissue had taken up the space usually inhabited by the cochleo-vestibular nerves, as well as causing the loss of the spiral ganglion neurons from the cochlear modiolus. This likely explains the patient's progression to total deafness, and perhaps exemplifies why brainstem implants rather than cochlear implants may be more effective for people with advanced and aggressive forms of NF2-SWN (Sanna et al., 2012). The more extensive internal destruction and remodelling of the left ear (Fig. 6) demonstrates the need for early treatment in some cases – untreated tumours may advance throughout the inner ear, and even into the middle ear, making complete surgical removal almost

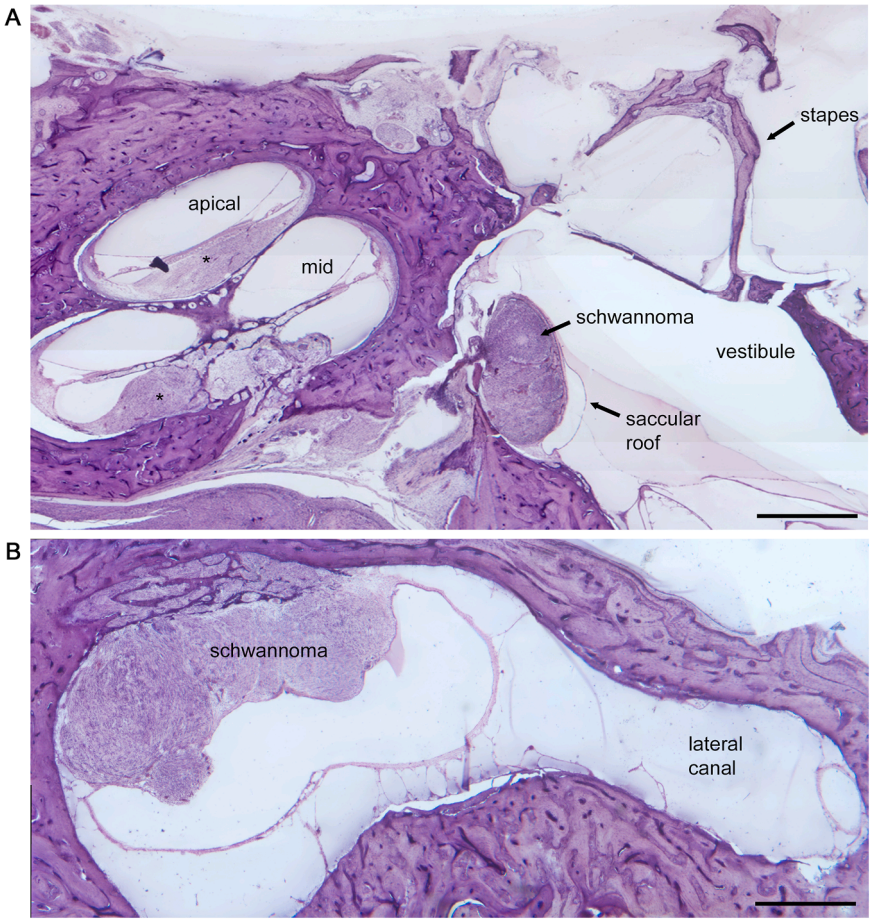

Fig. 4. Tumours within the right vestibular system of a 40-year-old male with NF2-SWN.
A, An oval-shaped schwannoma in the vestibule distorts the saccular macula (sensory epithelium). The stapes is in its normal position. Schwannomas are apparent in the cochlea (labelled *). **B,** A multi-lobulated schwannoma fills the region normally occupied by the utricular macula and the crista ampullaris of the lateral semi-circular canal. UCL case F15; haematoxylin and eosin staining.
Scale bars: **A & B**, 1 mm.

impossible.

3.3. *Insights into NF2-SWN and the ear: two young female case studies*

In 1933 Gray reported on two young females, a 21-year-old and a 14-year-old, whose symptoms were both consistent with a diagnosis of NF2-SWN (Gray, 1933). On the first case, for which we do not have the temporal bones, Gray reported her on admission in April 1929 to be "*blind, deaf, indolent but contented and puerile*". There was a slight facial paralysis, and signs of dysfunction of several cranial nerves. The patient died in the September of that year having suffered difficulties with respiration. In the post-mortem notes Gray summarised that the case "*was one of von Recklinghausen's disease, of the central type, there being no tumours on the peripheral nerves. There were typical tumours of the papillae of the eyes, and of the acoustic nerve on both sides.*" Photomicrographs of the right and left temporal bones revealed large tumours in both the internal auditory canals. A tumorous mass was evident in the apical region of the right modiolus, and in scala tympani in the basal region of the left cochlea. The spiral ganglion neurons were fewer in number than normal in both ears, but both of the organs of Corti appeared largely unaffected. Notably, in both ears there were symmetrical areas of oto-sclerotic bone in the region of the otic capsule just anterior to the oval window, and adjacent to the footplate of the stapes. This bone appeared to have a high marrow content. In the right ear the new bone had spread to the anterior crus of the stapes, causing its fixation.

The 14-year-old female (UCL case F25, detailed here in Fig. 7) first became apparent to the consulting surgeon of the Westminster Hospital ENT department in May 1931. The girl experienced symptoms of severe occipital headaches on her right side, worsening when recumbent, and vomiting and dizziness on sudden movement. She was admitted to hospital for testing in August 1932 after noting deafness occurring in her right ear. There were symptoms of ataxia and weakness of her right limbs, occasional attacks of double vision and a tendency to fall to the right when unbalanced. Her fifth and seventh cranial nerves were considered healthy. A Rinne test was performed and came back as negative on her right, suggesting a conductive hearing loss on that side. The girl had developed horizontal and vertical nystagmus by September of the same year. The tympanic membrane of the right ear was normal, but still with a negative Rinne test, though by now there was also a "*considerable degree of nerve deafness on that side*". Caloric tests showed the right labyrinth was inactive and the left responses were delayed. Hearing tests carried out on the left ear came back normal. The patient died in November 1932, with no stated cause of death. Numerous small tumours were found under the skin during the post-mortem, and a tumour the size of a hen's egg was found in the cerebello-pontine angle on the right, and one the size of a cherry on the left cochleo-vestibular nerve. The medulla and pons had been pushed over to the left due to the large tumour on the right side, and the lateral ventricles and the fourth ventricle were dilated.

Only the left temporal bone was available for inspection (there is no explanation as to why the presumably more affected right bone was unavailable). There was a large schwannoma occupying the left inferior

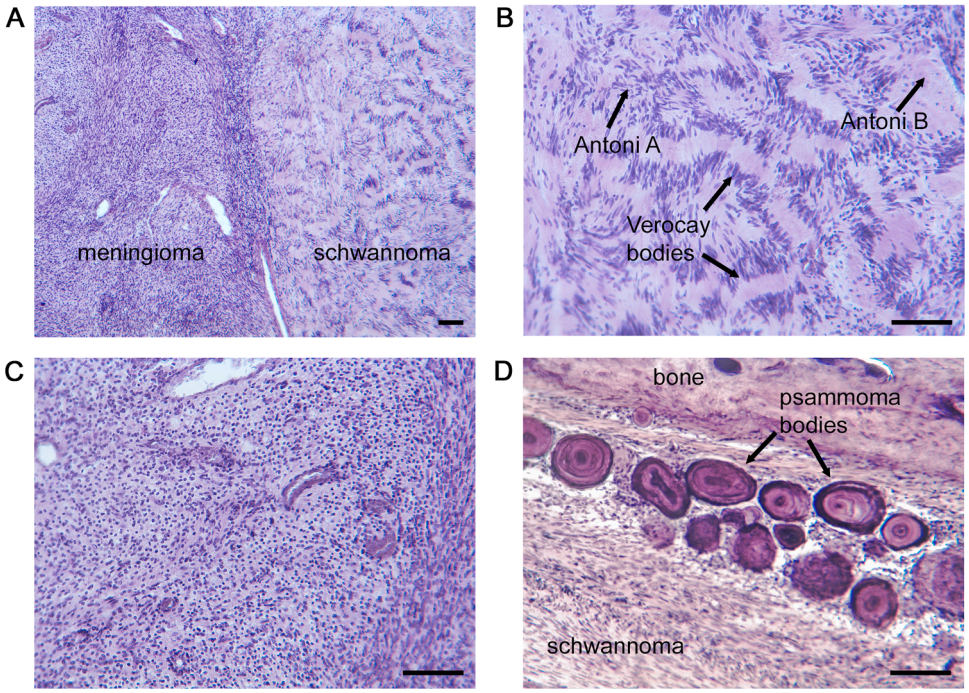

Fig. 5. Histological hallmarks of NF2-SWN tumours.
A, Distinct neoplasms identified as a schwannoma (right) and a meningioma (left) are in close apposition within the internal auditory canal. **B,** Within the schwannoma some nuclei form ordered palisade layers, creating regions with relatively higher cytoplasmic content typical of Verocay bodies. High cell density Antoni type A and low-density type B regions are evident. **C**, The meningioma is densely populated by cells with round nuclei and is highly vascularised. **D**, In the cerebello-pontine angle, lying between a schwannoma and the cochlear bony capsule are numerous psammoma bodies, with diameters ranging 30–150 μm. UCL case F15, right ear; haematoxylin and eosin staining. Scale bars: **A-D**, 100 μm.

vestibular nerve (Fig. 7A). There were no gross changes to the organ of Corti and spiral ganglion within the middle or apical turns, beyond those expected by post-mortem autolysis, consistent with the normal hearing tests on the left side two months before the patient's death. The largest changes were seen in the basal turn of the cochlea where neurons were fewer in number (Fig. 7B). Tumour tissue was found on the lower surface of the osseous spiral lamina in this region, and this extended along the wall of scala tympani (labelled 1 and 2, respectively, in Fig. 7B, and highlighted in Fig. 8 of Gray's original study). These may have arisen at or close to these locations, rather than having spread from the cochlear nerve which appeared free of tumours (Fig. 7A,C). Multi-lobular tumours were found in the semicircular canals. Notably, there was an "*existence of an area of otosclerotic bone in front of the oval window*" (Fig. 7D; equivalent to original Fig. 7). This was porous in texture, with bone marrow present within the large spaces. It also "*absorbed haematoxylin stains with avidity*", and so appeared darker than the surrounding bone. It had not invaded the stapedio-vestibular articulation, and consequently no ankylosis of the joint occurred. There were no noted pathological changes to the middle ear in the left temporal bone.

These two young female patients shared a number of inner ear phenotypes typical of NF2-SWN (described by Gray as "*multiple*" or "*central*" neurofibromatosis). Both had bilateral vestibular schwannomas, with progressive hearing loss and signs of imbalance. The tumours invaded various regions of the inner ear, causing regionalised loss of ganglion cells but left the organ of Corti largely undamaged. In one case (F25) it appeared that, unusually, tumours had arisen locally within the cochlea, rather than having migrated from the nerve. Common to both cases, and noteworthy to Gray, were the areas of otosclerotic bone in front of the oval window. He remarked that it was "*distinctly uncommon for otosclerosis to occur in early life*" and given that both conditions were relatively rare, it seemed to him more than chance that they should occur together in the same patients.

3.4. Is there a link between bilateral schwannomas and otosclerosis?

The pathophysiology of otosclerosis remains poorly understood despite many years of scientific and clinical research. Otosclerosis is considered a complex disease involving a number of environmental and genetic etiological factors (Rudic et al., 2015). Albert Gray suspected that in his three cases of "*central neurofibromatosis*" the otosclerosis-like bone growth may have been the result of "*a defect in the reflex arc upon which depends the nutrition of the organ of hearing, and that the changes in the bone and in the cochlear nerve are two of the effects which may occur when that reflex fails*" (Gray, 1933). He continued: "*The slowly growing tumours on the acoustic nerves must interfere in some way with the nerve fibres involved in the reflex arc. This would account for the changes in bone which present all the features of those found in typical otosclerosis*". He summarised that "*it is of course within the bounds of possibility that there is no relationship between the occurrence of the acusticus tumours and that of the otosclerotic bone…but it is in the highest degree improbable that such is a correct interpretation of the facts*". Gray's hypothesis that new bone growth could result from a degenerative process of the cochleo-vestibular nerve itself was thrown into doubt by studies in the following years. Otosclerotic foci close to the oval window were not found in cases of unilateral "*acoustic tumors*" (Fowler, 1936) or bilateral "*auditory nerve tumours*" (Scott, 1938), leading both of these authors to suggest Gray's observation of the two pathologies together may be coincidental. Linthicum and Brackmann reported a case of bilateral schwannomas in which there was intra-cochlear bone growth comparable to that seen in the 40-year-old male patient here (Fig. 6A,C), which they proposed was due to an interrupted blood supply (Linthicum and Brackmann, 1980).

The unusual finding of "*acoustic tumours*" in seven patients with otosclerosis, including one with "von Recklinghausen's disease" (Clemis, 1973), highlighted the importance of considering dual pathologies when sudden hearing loss affects an otosclerotic ear. Of 8500

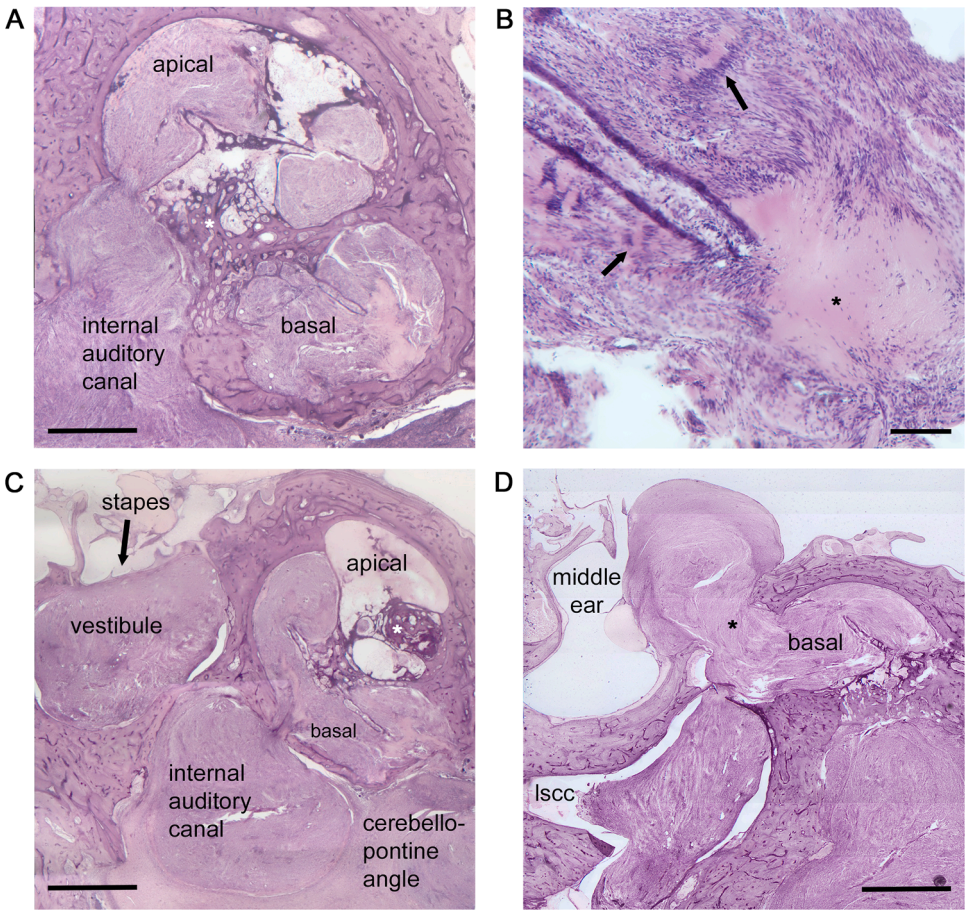

Fig. 6. The left ear of a 40-year-old male with NF2-SWN.
A, Schwannomas fill the internal auditory canal and the majority of the cochlea. New regions of highly stained bone are evident within the cochlea (*). **B,** The schwannoma within the basal cochlear region is mostly densely cellularised (Antoni type A) and has Verocay bodies (arrows). A less dense (Antoni type B) region is evident (*). **C,** In another section, schwannomas are also seen within the cerebello-pontine angle and the vestibule. The tumour pushes the stapes outwards. New bone is evident in the apical cochlear region (*). **D,** A schwannoma escapes from the cochlea through the round window (*) into the middle ear and extends towards the lateral semi-circular canal (lscc). UCL case F15; haematoxylin and eosin staining. Scale bars: **A, C-D**, 1 mm; **B**, 100 μm.

otosclerosis patients seen in that clinic, only three acoustic neuromas had been found in that group (<0.1 %). However, Clemis reported that of his first 59 "*acoustic tumor*" patients, four had otosclerosis (~7 %). Consequently, he summarised "*while the incidence of acoustic neuroma in an otosclerosis population is a most unusual occurrence, the reverse is not so true, and there could be more than just a casual association between the two diseases*". Given there is evidence for co-existing bilateral schwannomas with otosclerosis within the more recent literature (Nam et al., 2011), this may be an area for further study. That notwithstanding, additional causes of conductive deafness could be considered in cases of NF2-SWN (see Section 4).

4. How do NF2-SWN tumours affect the tissues of the human inner ear?

What can other temporal bone studies tell us about the aetiology of hearing loss and imbalance in NF2-SWN? Numerous mechanisms have been proposed to underlie hearing loss in NF2-SWN, based on the location of bilateral schwannomas and meningiomas within the inner ear. These include conductive losses due to stapes fixation, intra-labyrinthine haemorrhage, endolymphatic hydrops, interruption of the cochlear blood supply, and changes of the chemical make-up of the inner ear fluids (Asthagiri et al., 2012). Several of these pathologies could contribute to the widely reported losses of sensory cells, but also to the disruption of non-sensory tissues that ensure normal inner ear homeostasis. To provide a consensus view of the inner ear landscape in this complex disease, below we summarise published temporal bone reports that describe the histological features of bilateral vestibular schwannomas and their effects on key tissues.

4.1. What is the origin of bilateral tumours in NF2-SWN?

The bilateral tumours associated with NF2-SWN arise from Schwann cells (not neurons) in the cochleo-vestibular nerve, most commonly within the vestibular branches (Bustamante-Balcarcel and Barrios del Valle, 1983; Coy et al., 2020; Stivaros et al., 2015). Both these facts mean that the previously used term "*acoustic neuroma*" may be misleading. MRI imaging in paediatric NF2-SWN patients has shown there is no particular predilection for the superior or inferior branches of the vestibular portion of the nerve (Stivaros et al., 2015). Such imaging shows that NF2-SWN patients may have numerous discrete tumour nodules, and it seems likely that the single large tumours observed in more advanced cases have coalesced from multiple loci at earlier pre-symptomatic stages of the disease (Dewan et al., 2015; Stivaros et al., 2015). Multi-lobulated tumours within the internal auditory canal are reported in several studies (Benitez et al., 1967; Bustamante--Balcarcel and Barrios del Valle, 1983; de Klejn and Gray, 1932; Doherty et al., 2014; Gray, 1933; Grobman et al., 1990; Linthicum and Brackmann, 1980; Nam et al., 2011; Scott, 1938; Sobel, 1993; Stivaros et al., 2015). The reduced numbers of auditory nerve fibres in cases where the tumours are very large could cause sensorineural hearing loss in these patients. In more aggressive Wishart-type cases the tumours may invade

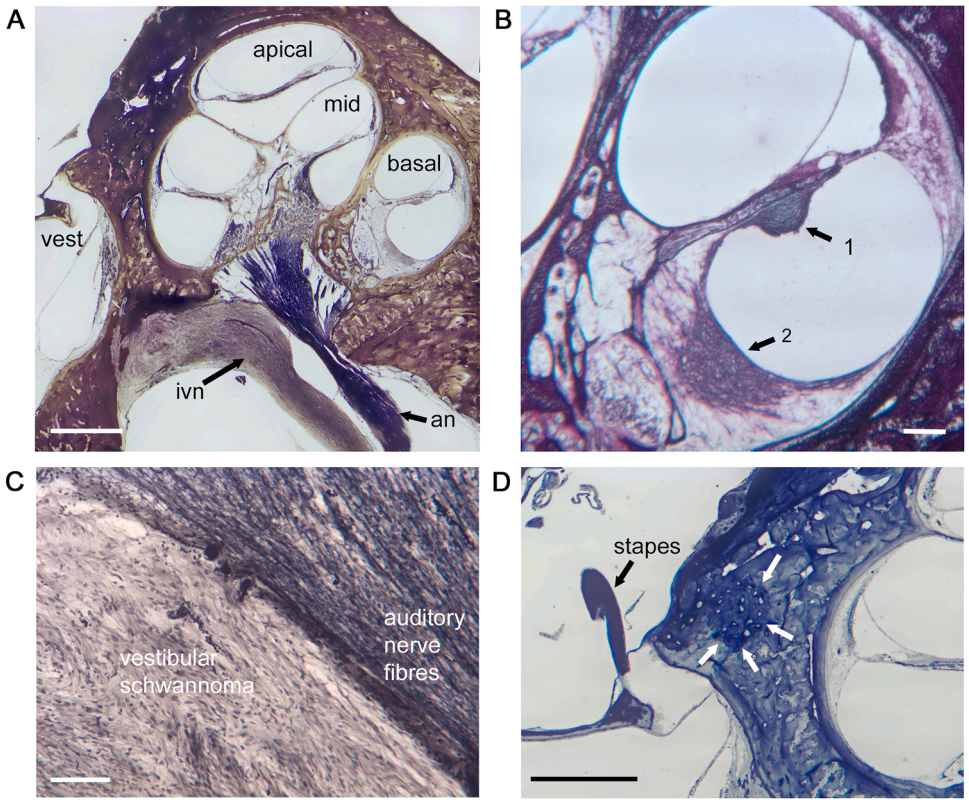

Fig. 7. The inner ear of a 14-year-old female with "central neurofibromatosis" (NF2-related schwannomatosis).
A, A mid-modiolar section stained using Kulchitsky's modification of Weigert Pal (for myelin). A schwannoma is spread throughout the inferior vestibular nerve (ivn) but the auditory nerve (an) is well-populated with myelinated nerve fibres. Spiral ganglion neurons are evident in good numbers within the mid-turn region of Rosenthal's canal. **B,** In the basal cochlear region there are tumours under the lower surface of the bony spiral lamina (1) and extending from the modiolar wall into scala tympani (2). There are very few spiral ganglion neurons in this region. **C,** Detail of a region in the internal auditory canal where a schwannoma in the inferior vestibular nerve lies adjacent to the apparently unaffected auditory nerve. **D,** A clearly demarcated region of new bone growth is evident close to the oval window (arrows). The stapes is mis-positioned following the removal of the temporal bone during the post-mortem. **B-D** stained with haematoxylin and eosin. UCL case F25, left ear. Scale bars: **A** & **D**, 1 mm; **B** & **C**, 100 μm.

the internal auditory canal bony wall (DeMoura et al., 1969; Doherty et al., 2014; Linthicum, 1972; Linthicum and Brackmann, 1980), and this is associated with poorer hearing (Doherty et al., 2014).

Light microscopy analysis in a number of other NF2-SWN cases has identified the histological features that we show here. These include predominantly Antoni type A regions, regions with palisaded elliptical nuclei and Verocay bodies and also numerous psammoma bodies (DeMoura et al., 1969; Fowler, 1936; Gardner and Turner, 1940; Linthicum and Brackmann, 1980; Nam et al., 2011; Scott, 1938; Sobel, 1993). The observations here thus identify the characteristic features of the bilateral schwannomas that are the hallmarks of NF2-SWN. Meningiomas have been reported widely (Flexon et al., 1991; Linthicum and Brackmann, 1980; Nam et al., 2011; Scott, 1938; Sobel, 1993), and these may be adjacent to, or fused with a schwannoma to form a "composite" tumour.

4.2. *Where else are NF2-SWN tumours found in temporal bones?*

As described in Section 4.1 it is likely that the tumours in NF2-SWN have numerous sites of origin (Dewan et al., 2015; Stivaros et al., 2015), and so multiple discrete tumours could be identified in a single temporal bone section, or alternatively there may be larger masses formed by the fusion of several migrating growths. As seen elsewhere in the literature, schwannomas are sometimes found within cochlear structures such as the bony modiolus, either within Rosenthal's canal where the spiral ganglion neurons are normally housed (Linthicum, 1972; Nam et al., 2011), but also escaping into the perilymph-filled compartments of scala tympani and scala vestibuli (Benitez et al., 1967; Bustamante-Balcarcel and Barrios del Valle, 1983; Flexon et al., 1991; Scott, 1938). We are unaware of tumours surviving within the endolymphatic compartment (scala media). We show that the tumours may enter the vestibule and semi-circular canals from the vestibular nerves, and this has been observed elsewhere (Benitez et al., 1967; Nam et al., 2011; Scott, 1938). Additionally, it has been suggested that "seedling" tumours may be found within the vestibule that are spatially isolated from the larger growths within the internal auditory canal (Benitez et al., 1967; Hallpike, 1963). Hallpike (1963) argued that tumours in the vestibule could cause a conductive hearing loss where the footplate of the stapes becomes immobilised, but it seems likely that there would be a more dominant sensorineural loss in such cases caused by schwannomas associated with the cochleo-vestibular nerves.

De Klejn and Gray described how a vestibular schwannoma grew through and destroyed the petrous bone, eventually reaching and lying against the carotid artery (de Klejn and Gray, 1932), a feature of NF2-SWN tumours described elsewhere (Bustamante-Balcarcel and Barrios del Valle, 1983). This pathology may contribute to the morbidity of the disease by a compression of the blood supply to the brainstem, but it also presents a significant difficulty for surgical removal of tumours that migrate there (Ghalavand et al., 2023). Similarly, schwannomas grow close enough to the facial nerve to compress it, and it is not unusual for tumours to be found growing on the facial nerve itself (de Klejn and Gray, 1932; Flexon et al., 1991; Linthicum and Brackmann, 1980; Nam et al., 2011; Stivaros et al., 2015). Either of these two effects may lead to facial paralysis.

4.3. What are the effects on individual tissues?

Bilateral vestibular schwannomas associated with NF2-SWN are reported to have different effects on the auditory nerve compared to those from sporadic unilateral schwannomas. Unilateral tumours arising on the vestibular nerve typically compress the cochlear nerve fibres and rapidly cause auditory deficits (Linthicum and Brackmann, 1980). Bilateral tumours, though, are often slower to reveal their presence because they can grow between the nerve fibres without compressing them. The cochlear nerve may function normally until the tumour is very large, and this may help explain a lack of correlation between tumour size and the degree of hearing loss (Asthagiri et al., 2012; Linthicum, 1972).

A loss of cochlear hair cells and spiral ganglion neurons are common observations in temporal bone studies of NF2-SWN. There are examples in the literature where neurons have been lost, but hair cells remain at the time of death (DeMoura et al., 1969), suggesting that there may be phased losses of specific cell types, and that neuronal loss does not inevitably lead to hair cell loss. The consistent observation of widespread auditory nerve fibre loss is a clear demonstration of the challenge that NF2-SWN poses for treatment of a patient's hearing loss. In such cases the use of neither hearing aids nor cochlear implants may bring therapeutic benefit, and auditory brainstem implants are more likely to be an effective strategy (Sanna et al., 2012). Tumours on the vestibular nerve can also cause the destruction of the vestibular (Scarpa's) ganglia and their associated neurites/axons (Benitez et al., 1967).

Atrophy and changes to the structure of stria vascularis, particularly vacuolisation and swelling, have been observed by others (Benitez et al., 1967; DeMoura et al., 1969; Flexon et al., 1991; Nam et al., 2011). These changes could lead to a dysregulation of the cochlear fluids, possibly causing an endolymphatic hydrops and contributing to Ménières-like symptoms. Indeed, endolymphatic hydrops has been reported in cases of bilateral schwannomas (DeMoura et al., 1969; Flexon et al., 1991). There have been numerous reports of acidophilic or granular proteins within the perilymphatic or endolymphatic compartments (Benitez et al., 1967; DeMoura et al., 1969; Flexon et al., 1991; Hallpike, 1963; Nam et al., 2011; Scott, 1938). In Hallpike's report of a schwannoma in the vestibule of a young male with "*generalised neurofibromatosis or von Recklinghausen's disease*" he pointed out that within the cochlea there was "*distention of the scala media (hydrops) with albuminoid coagulum in the scala vestibule*". The reasons why such proteins might commonly appear in the cochlear fluids are not clear, and so their origin, identity and pathological significance remain areas that deserve further study.

5. Summary

Light microscopy studies of human temporal bones over the past 100 years have revealed commonalities between cases of NF2-SWN. The vestibular schwannomas and meningiomas that characterise this complex disease can cause the death of sensory cells within the cochlea and vestibular organs that underlie permanent hearing loss and imbalance. Aggressive tumours can also eat-away sizeable bony structures to compress major cerebral blood vessels, and they can cause deformation of important brain areas. Left unchecked, these neoplasms have the potential to cause life-changing effects within the central nervous system. There is often a clinical "watch and wait" approach in cases with less aggressive and smaller tumours (Forde et al., 2021; Ren et al., 2021; Ruiz-Garcia et al., 2024), but the younger NF2-SWN patients with the more aggressive Wishart-type NF2-SWN will eventually require surgery. Recent years have seen advances in the understanding of the underlying genetics and molecular signalling pathways associated with pathogenic variations in *NF2*, and this has led to the development of experimental and clinical interventions aimed towards limiting tumour growth (Franco-Caspuenas et al., 2025; Ghalavand et al., 2023; Laraba et al., 2023; Plotkin et al., 2009; Ren et al., 2021; Ruiz-Garcia et al., 2024; Vlashi et al., 2024). Earlier diagnosis coupled with specific therapies in dedicated treatment centres are resulting in improved patient survival (Forde et al., 2021; Hexter et al., 2015). Continued experimental studies and the resulting clinical trials will undoubtedly lead to further developments that will enhance the life-quality and lifespan of people living with NF2-SWN.

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Eleanor D. Brown: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Shada Nassar:** Writing – review & editing, Investigation. **Daniel J. Jagger:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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Data availability

Data will be made available on request.

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