Introduction

Xeroderma pigmentosum (XP) is a rare, autosomal recessive genetic disease occurring throughout the world. In the US and Europe, the prevalence is about 1 per one million, while XP is more frequent in Japan and parts of Africa. XP patients are hypersensitive to sun exposure and have defective repair of sunlight-induced DNA damage. Approximately 50% of XP patients have a history of severe burning on minimal sun exposure. Most XP patients develop myriad of freckle-like pigmented lesions on sun-exposed skin early in life—often before 2 years of age. Continued sun exposure often results in skin having the appearance of premature aging with areas of increased pigment, decreased pigment, atrophy and telangiectasia. XP patients seen at the National Institutes of Health (NIH) Clinical Center since 1971 had a more than 10,000-fold increased risk of developing skin cancer before 20 years of age (1). Rarely, patients with XP also have features of Cockayne syndrome with short stature, sun sensitivity, progressive retinal degeneration, hearing loss and dysmyelination of the brain (2). XP is heterogeneous at the molecular and genetic level, resulting from different defects in the nucleotide excision repair (NER) pathway. Seven XP complementation

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groups (genes), known as XP-A through XP-G, are associated with defective NER. An additional group, the XP variant, has a defect in DNA polymerase eta, which is involved in translesional DNA synthesis.

Approximately 25% of the 106 XP patients seen at the NIH Clinical Center developed progressive neurological degeneration (1). These patients often have defects in the XP-A, XP-B, XP-D or XP-G genes, although not everyone in these complementation groups will develop the neurologic phenotype. The clinical presentation of those with XP-related neurological degeneration includes loss of intellectual functioning, abnormal speech, areflexia, ataxia, peripheral neuropathy, progressive sensorineural hearing loss and loss of ability to walk and talk. XP patients with neurologic degeneration had poorer survival than those patients who had no neurologic degeneration. Among the earliest clinical indications of progressive neurological degeneration are absent deep tendon reflexes and sensorineural hearing loss.

Auditory Function in Persons with XP

We recently conducted a retrospective study of hearing in 79 patients, aged 1-61 years, seen at the NIH Clinical Center between 1971-2012. All met clinical criteria for diagnosis of XP (n=77) or XP/Cockayne syndrome complex (n=2). XP complementation groups were established via genetic testing. Patient data were extracted from NIH Clinical Center medical records, records of outside institutions, and personal correspondence.

Clinically significant hearing loss (5/1/2/4-kHz pure-tone average >20 dBHL was observed in 29% (n=23/79) of the NIH XP cohort, and this hearing loss was sensorineural in 23%, conductive in 1%, and of undetermined type (due to lack of bone conduction audiometry) in 5%. Among the complementation groups we studied, those with XP-C had the highest proportion of normal hearing (89%), and no one in this group had XP-type neurologic degeneration. Complementation groups XP-A and XP-D had the highest prevalence of hearing loss at 44% (n=4/9) and 53% (n=9/17) respectively.

We were interested to know if there was an association between sensorineural hearing loss and XP-type neurologic involvement. Within the NIH cohort, 70% (n=55) had no neurologic involvement, and 89% (n=49) of this group had normal hearing. XP-type neurologic involvement was present in 29% (n=17), and a large proportion (76%; n=13) of this group had clinically significant hearing loss ($\chi^2$P<0.0001) A small number (n=7)
had non-XP type neurologic involvement attributable to other factors (e.g. fetal alcohol syndrome), and three of these patients had hearing loss (Fig. 1).

Mean age of onset of sensorineural hearing loss in those with XP-type neurologic degeneration was 19 years, and all patients with longitudinal data developed clinically significant hearing loss by 24 years of age, except for four normal hearing patients who were not tested past 16 years of age. Progression from a mild to severe or profound degree typically occurred within a 20-year period. Examples of hearing loss progression are shown for two patients with XP-type neurologic degeneration (Fig. 2) for whom otopathology results are presented in the following section.

Prediction of patients with XP who will develop XP-like neurological degeneration is clinically useful but challenging. Audiometric status, XP complementation group and acute burning on minimal sun exposure are important early indicators of XP-like neurological degeneration. Totonchy, et al. (5) showed that degree of hearing loss is directly correlated with neurological involvement. Patients with XP-type neurological degeneration showed a 54-year reduction in the age at which clinically significant hearing loss was documented in relation to a population without XP.

Cochlear histopathology in patients with XP-type neurodegeneration

**XP-Neurologic Phenotype XPA (XP12BE):**
This patient had a progressive down sloping sensorineural loss with marked reduction in speech discrimination scores bilaterally. The organ of Corti was either missing or reduced to a mound of undifferentiated cells in the basal and lower middle turns. Some inner and outer hair cells were present in the upper middle and apical turns on both sides. There was patchy, moderate to severe atrophy of the stria vascularis in all three turns. There was severe loss of cochlear neurons in all turns (Fig. 3). There was degeneration of Scarpa’s ganglion bilaterally.

**XP-Neurological Phenotype XPD (XP18BE):**
This patient had a bilateral progressive down sloping sensorineural loss. A final audiogram at age 40 showed severe to profound loss in both ears with speech discrimination scores of 0% bilaterally.

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Unlike the findings in those without neurological degeneration (5), the organ of Corti was completely devoid of inner and outer hair cells, and there was patchy atrophy of the stria vascularis. There was severe loss of cochlear neurons and in particular dendritic fibers compared to age-match controls (Fig. 4).

The histopathologic correlate of the sensorineural loss in the neurologic phenotypes was degeneration of the organ of Corti and spiral ganglion cells (6). It is not possible to determine whether the loss of spiral ganglion cells was primary or secondary, but given severe degeneration of the cochlear neurons despite the preservation of some hair cells in the apical half of the cochlea in the XPA variant suggests primary neuronal degeneration was operant.

Discussion

The otopathologic changes observed in the two cases presented herein both show atrophy of the organ of Corti, stria vascularis and spiral ganglia in two patients with XP-type neurological degeneration and sensorineural hearing loss that progressed from severe to profound by the third decade of life. While it remains unknown if spiral ganglia degeneration preceded or followed loss of the neuroepithelial cells, the histopathology identifies a combined cochlear and neural origin of the hearing loss. DNA repair appears to be critical in maintaining integrity of the auditory system.

Patients diagnosed with XP-A, XP-B, XP-D or XP-G genes are at risk for developing neurological degeneration. Prediction of individuals within these complementation groups who will go on to develop neurologic degeneration is clinically challenging. Data from the NIH-XP cohort suggests that degree of hearing loss is directly correlated with neurological involvement, and that onset of sensorineural hearing loss at a young age is a clinical predictor for possible neurologic degeneration. Regular audiometric evaluation may serve as a means of early identification of XP-type neurologi
cal degeneration (4). Furthermore, patients at risk for progressive sensorineural hearing loss require close audiologic monitoring to facilitate timely intervention with amplification and other rehabilitative measures.

REFERENCES


FIGURE LEGENDS

Figure 1. Worse-hearing ear four-frequency pure-tone average (4F PTA; 0.5, 1, 2, 4 kHz) plotted against the percentiles obtained from age-matched normative data [see ref. 3] and the criterion for clinically normal hearing (≤20 dB HL). Neurological status: XP-type neurological degeneration, non-XP type neurological involvement and patients with XP without neurological involvement, is indicated by color-coding. Filled symbols represent males and open symbols represent females.

Figure 2. Longitudinal pure-tone air-conduction audiograms and degree of neurological involvement for (A) patient XP12BE with XP-A and (B) patient XP18BE with XP-D. Both had XP-type neurological involvement. Neurologic status is color-coded: blue = no neurological involvement; purple = gait disturbance due to spasticity or ataxia, moderate mental retardation (IQ<50); red = severe mental retardation; cannot walk, cannot speak and/or activity limited to bed rest.

Figure 3. Otopathology of XP – Neurological Phenotype XPA (XP12BE) patient.

Figure 4. Otopathology of XP – Neurological Phenotype XPD (XP18BE) patient.
The Royal Victorian Eye and Ear Hospital and the Department of Otolaryngology at the University of Melbourne have joined forces to establish Australia’s first temporal bone bank. Building upon Melbourne’s long research and clinical interests in cochlear implantation, the temporal bone bank will also focus upon neuro-otological histopathology.

Current initiatives in cochlear implant otopathology and vestibulopathology are underway.

**Cochlear Implant Otopathology**

In recent years, our primary research interest in Melbourne has been otoprotection in the context of cochlear implantation (1) (2) (3). This has prompted a reappraisal of the cochlear histopathology of inner ear surgery. Some interesting questions that now need to be addressed include an elucidation of the causes of hearing loss after electrode insertion, mechanisms of delayed hearing loss, and the effects of protective agents such as steroids on hearing and the tissue response to implantation.

Using micro-CT imaging techniques adapted from Wong and colleagues (4), we are gaining new insights into the nature of the fibrosis that accompanies electrode insertion. Guinea pig temporal bones have been fixed in osmium tetroxide and imaged to reveal in detail both the electrode track and the fibrosis that accompanies electrode insertion. Osmication increases the radiodensity of the soft tissues within the inner ear so that these can be seen more easily on the CT-scanned images, including the organ of Corti and Reissner’s membrane (Fig. 1a). Note that the auditory neurons and lateral wall are particularly well stained. It is apparent from Fig. 1b that the fibrosis is very broadly based, extending in this cochlea from the lateral scalar walls towards the implant, a perspective not so well appreciated from histological sections. Micro-CT makes quantification of the electrode tract, and the shape and extent of the tissue response easier. In keeping with previous studies in human and feline temporal bones, we have shown using conventional histology that a more extensive tissue response is associated with poorer local survival of hair cells and spiral ganglion cell neurons (5). Interestingly, a greater extent of tissue response is also associated with poorer auditory brainstem response thresholds in cochlear regions apical to the position of the electrode (5). It is not yet clear whether the fibrosis disrupts this hearing by disturbing cochlear mechanics, or whether both the fibrosis and the hearing loss reflect the degree of cochlear inflammation experienced in the postoperative period.

Delayed hearing loss after cochlear implantation has proven to be a major impediment for electroacoustic hearing. This is

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typified by deterioration in acoustic thresholds in the first few months after cochlear implantation, often rendering the residual hearing unaidable. Delayed hearing loss occurs in up to a third of patients who have undergone otherwise successful hearing-preservation cochlear implantation. A similar phenomenon can be observed in guinea pigs after cochlear implantation, so we have explored whether the extent of the tissue response to the cochlear electrode is associated with delayed hearing loss. We find that delayed hearing loss is seen only when the tissue response is extensive. Auditory brainstem response thresholds may actually improve over time when there is minimal fibrosis (5). We infer from these findings that more extensive inner ear injury is one potential mechanism for delayed hearing loss.

In view of the considerations above, it may be advantageous to seek to reduce the extent of fibrosis in the implanted cochlea. Glucocorticosteroids have been shown to protect hearing in several experimental models of cochlear implantation, so it is of interest to know whether these agents also modify the tissue response. Recently, we have compared the extent of fibrosis surrounding the implant after the administration of either local or systemic steroids prior to electrode insertion. It was found that systemic, but not locally applied steroids reduced the amount of fibrosis within scala tympani (6). It seems, therefore, that steroids may not only improve hearing, but also modify the tissue response to surgery (although, the latter is influenced by the route of administration).

The Australian Temporal Bone Bank builds upon a small collection of human temporal bones within the Department of Otolaryngology, most of which were donated by cochlear implant recipients. We are looking forward to contributing further to cochlear otopathology through this new venture.

**Vestibulopathy**

We are also particularly interested in developing expertise in vestibular histopathology. A recent collaboration between our neurologist/neuro-otologist, Dr. David Szmulewicz and the Otopathology Laboratory at the Massachusetts Eye and Ear Infirmary demonstrates the potential benefits of the temporal bone bank for improving an understanding of vestibular disease. Several years ago, a group of patients were identified with cerebellar ataxia and an abnormal visually enhanced vestibular ocular reflex (VVOR), which is a compound impairment of the three key corrective oculomotor reflexes, namely smooth pursuit, the vestibulo-ocular reflex (VOR) and the optokinetic reflex (OKR). A peripheral neuropathy was found also to be integral to this syndrome that has subsequently been called Cerebellar Ataxia Neuropathy bilateral Vestibular Areflexia Syndrome (CANVAS) (7). It was not until the temporal bone and lower cranial nerves were examined that the histopathology was found to be a neuronopathy (ganglionopathy) of the vestibular, facial and trigeminal nerves (8). This is seen in Figure 2, where the vestibular nerve is seen to be atrophied, and there is a reduced neuronal density in Scarpa’s ganglion. This condition can now be diagnosed at the bedside through the advent of fast video goggles that allow for diagnosis of an impaired VVOR (9), and more than 60 patients, including nine kindreds, have been identified. Identification of the causative gene is now well underway.

We would like to thank MEEI, and in particular the late Saumil Merchant, whose enthusiasm and generosity encouraged us to proceed with plans to establish a temporal bone bank. We would also like to thank the NIH for allowing us to adapt the Temporal Bone Registry’s donor materials for use in Australia, to promote consistency in the patient information collected on each side of the Pacific. ■
FIGURE LEGENDS

Figure 1a. Micro-CT of a cochlear turn in the guinea pig following fixation in osmium tetroxide. Note the cochlear dummy electrode present within scala tympani in the lower basal turn.

Figure 1b. The tissue response to cochlear implantation, rendered from a micro-CT volume. The basal turn on the left cochlea is viewed from the round window looking apically, with the wall of scalar tympani in purple (medial side to the left). The electrode (blue) was inserted via a cochleostomy and is tracking along the lateral cochlear wall. The issue response (yellow) is broadly based, extending over a wide front from the lateral wall and spreading towards the electrode. These images are the work of Dr. Phillip Sale, from the Department of Otolaryngology, University of Melbourne.

Figure 2. The histopathology of the vestibular nerve in a case of CANVAS. The vestibular nerve is seen to be much more atrophic than normal, and the neuronal density in Scarpa’s ganglion is significantly reduced. This work was a collaboration between MEEI, Dr. Szmulewicz and colleagues in Australia. The sections were processed in the Otopathology Laboratory at the Massachusetts Eye and Ear Infirmary.

REFERENCES


Otopathology Mini-Travel Fellowship Program

The NIDCD National Temporal Bone Registry is pleased to announce the availability of mini-travel fellowships. The fellowships provide travel funds for research technicians and young investigators to visit a temporal bone laboratory for a brief educational visit, lasting approximately one week. The emphasis is on the training of research assistants, technicians and junior faculty.

These fellowships are available to:

• U.S. hospital departments who aspire to start a new temporal bone laboratory.
• Inactive U.S. temporal bone laboratories that wish to reactivate their collections.
• Active U.S. temporal bone laboratories that wish to learn new research techniques.

Up to two fellowship awards will be made each year ($1,000 per fellowship). The funds may be used to defray travel and lodging expenses. Applications will be decided on merit.

Interested applicants should submit the following:

• An outline of the educational or training aspect of the proposed fellowship (1-2 pages).
• Applicant’s curriculum vitae.
• Letter of support from temporal bone laboratory director or department chairman.
• Letter from the host temporal bone laboratory, indicating willingness to receive the traveling fellow.

Applications should be submitted to:
Michael J. McKenna, M.D.
NIDCD Temporal Bone Registry
Massachusetts Eye and Ear Infirmary
243 Charles Street
Boston, MA 02114
michael_mckenna@meei.harvard.edu
Free Brochures for your Office or Clinic about Temporal Bone Research and Donation

The Gift of Hearing and Balance: Learning about Temporal Bone Donation is a 16-page, full-color booklet that describes in more detail the benefits of temporal bone research. It also answers commonly asked questions regarding the temporal bone donation process. Dimensions: 7”x10”

If you would like to display either or both of these brochures, please complete the form below and return it to the Registry by mail or fax. The brochures will be sent to you free of charge. Please circle the amount requested for each brochure or write in amount not listed.

The Gift of Hearing and Balance _____ 25  50  100

Name: ______________________________________________________________________________________________
Address: ______________________________________________________________________________________________
City, State, Zip: _________________________________________________________________________________________
Telephone: ____________________________________________________________________________________________

Mail or fax this form to the Registry at: NIDCD National Temporal Bone, Hearing and Balance Pathology Resource Registry
Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114
Toll-free phone: (800) 822-1327, Fax: (617) 573-3838
Email: tbregistry@meei.harvard.edu