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3rd INTERNATIONAL SYMPOSIUM ON *INNER EAR THERAPEUTICS*

Inner Ear Therapeutics : Updates & Challenges for Applications

Program

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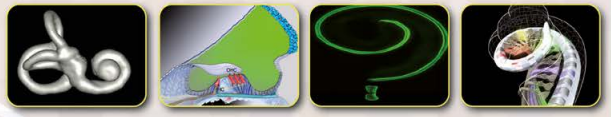

Recent Advances in the Management of Sensorineural Hearing Loss

28-30April MARRAKECH 2023
Kenzi Ménara Palace

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INNER EAR THERAPEUTICS: UPDATES AND CHALLENGES FOR APPLICATIONS

THURSDAY APRIL 27, 2023

17H30-19H30 REGISTRATION & WELCOME

DAY 1, FRIDAY APRIL 28, 2023

07h30–08h30 Registration

08h00–08h05 Welcome addresses / Introduction
Abdelaziz RAJI and **Saaid SAFIEDDINE**

08h05–08h20 **OPENING LECTURE**
Anne-Lise GIRAUD, Institut de l'Audition, Institut Pasteur, Paris, France.
Title: **Presentation of the Hearing Institute (IdA) and the re-Connect Project**

08H20-10H05 SESSION I

ADVANCING TOOLS FOR GENETIC SCREENING, CLINICAL INVESTIGATIONS AND DIAGNOSIS

Chairs: Jeffrey Holt, Aziz El Amraoui, Charles C. Della Santina

08h20–08h40 **Paul AVAN**, Institut de l'Audition, Institut Pasteur, Paris, France.
Title: **Eligibility to Gene Therapy: The Issue of Quantitative Assessment of Auditory Sensory Cells and Neurons**

08h40–09h00 **Sandrine MARLIN**, CRMR Surdités Génétiques AP-HP CHU Necker, INSERM, Paris, France.
Title: **New Technologies in Medical Genetics for Early Hearing Loss: Advances and Obstacles**

09h00–09h20 **Michael R. BOWL**, University College London Ear Institute, London, United Kingdom.
Title: **Background Check: Using the Mouse to Elaborate on the Genetics of Mammalian Hearing**

09h20–09h35 **Crystel BONNET**, Institut de l'Audition, Institut Pasteur, Paris, France.
Title: **Genetic Architecture of Prelingual Deafness in Saharan, Sub-Saharan and Middle East Populations**

09h35–09h50 **Nisrine ABOUSSAIR**, Genetic department Mohammed VI University Hospital, Marrakech, Morocco
Title**: The Frequency of the GJB2c.35 delG Mutation in Patients with Non-Syndromic Hearing Loss**

09h50-10h05 **Nish MEHTA**, University College London Hospitals NHS Foundation Trust, London, United Kingdom.
Title : **Data Science in Hearing Research**

10H05-10H30 COFFEE BREAK (POSTERS VISIT)

10H30-11H30 SESSION II

COCHLEAR IMPLANTATION: CHALLENGES AND PERSPECTIVES

Chairs: Ghizlene Lahlou, Thierry Mom, Abdulrahman Hagr

10h30–10h45 **Isabelle MOSNIER**, AP-HP Hôpital Universitaire Necker-Enfants-Malades, Paris, France.
Title: **Candidacy for Cochlear Implantation in Prelingual Profoundly Deaf Adult Patients**

10h45–11h00 **Farid ZAHRANI**, King Saud University Hospital, Ryad Saudi Arabia.
Title: **Effect of Radiological Grade of Cochlear Ossification on Cochlear Implant Outcome in Postmeningitis Deafness**

11h00–11h15 **Christophe VINCENT**, Centre hospitalier universitaire de Lille, Lille, France.
Title: **Evaluation of the Post-Implant Cochlear Fibrotic Reaction**

11h15–11h30 **Abdulrahman HAGR**, King Saud University Hospital, Ryad, Saudi Arabia.
Title: **Day Surgery for Cochlear Implantation under Conscious Sedation with Same-Day Fitting**

11h30-11h40 **Abdelaziz RAJI,** Mohammed VI University Hospital, ENT HNS department, Marrakech, Morocco.
Title: **Post Meningitis Hearing Loss from Screening to Hearing Rehabilitation**

11H40- 12H25 MED-EL SYMPOSIUM

MED EL

12H25-14H00 LUNCH BREAK AND POSTERS VISIT

14H00-15H15 SESSION III

REGENERATIVE AND DRUG-BASED THERAPIES FOR HEARING IMPAIRMENT

Chairs: Christine Petit , Bernard Fraysse, Sedigheh Delmaghani

14h00–14h20 **Thomas LENARZ**, Department of Otolaryngology, Hannover Medical School, Hannover, Germany.
Title: **Extracellular Vesicles in Inner Ear Therapies: Pathophysiological, Manufacturing, and Clinical Considerations**

14h20–14h40 **Athanasia WARNECKE**, Department of Otorhinolaryngology, Head and Neck Surgery Hannover Medical School, Hannover, Germany.
Title: **Perilymph Diagnostics: A New Possibility for the Development of Precision Treatment?**

14h40–14h55 **Marta ROCCIO**, Inner Ear Stem Cell Lab, Department of Otorhinolaryngology Head and Neck Surgery, University Hospital Zurich and University of Zurich, Switzerland.
Title: **Human Inner Ear Organoids: A New Tool to Probe Hearing Restoration Therapeutics**

14h55–15h15 **Jonathan KIL**, Sound Pharmaceuticals, Seattle, USA.
Title: **Ebselen (SPI-1005) Treatment Improves Hearing Loss and Speech Discrimination in Meniere's Disease**

15H15-16H00 REGENERON SYMPOSIUM

REGENERON
science to medicine®

16H00-17H00 COFFEE BREAK (POSTERS VISIT)

17H00-18H00 SESSION IV

PROBING THE RESIDUAL HEARING DURING SURGERY

Chairs: Isabelle Mosnier, Christophe Vincent, Fouad Benariba

17h00–17h15 **Thierry MOM**, Centre Hospitalier Universitaire, Clermont-Ferrand, France.
Title: **Fluoroscopy Guided and Robotized Cochlear Implantation : Optimized Control of Electrode-Array Insertion**

17h15–17h30 **Naima DEGGOUJ**, Cliniques Universitaires Saint-Luc, Brussels, Belgium.
Title: **Electrocochleography and Hearing Preservation in Cochlear Implantation**

17h30–17h45 **Shin-Ichi USAMI**, Shinshu University School of Medicine, Nagano, Japan.
Title: **The Challenges in Preserving Residual Hearing in Cochlear Implantation**

17h45–18h00 **Adrian ESRHAGHI**, University of Miami Ear Institute, University of Miami Miller School of Medicine, Miami, USA.
Title: **Dexamethasone Eluting Electrode and Drug A Acts Synergistically to Preserve Residual Hearing in an Animal Model of Cochlear Implantation**

18H00-19H00 OFFICIAL INAUGURATION

Chairs : Saaid Safieddine, Abdelaziz Raji

18h00-18h20 **A word of the dean and the president**

18h20-19h00 **Charles LIBERMAN**, Harvard Medical School, Mass Eye and Ear Infirmary, Boston, USA.
Title: **"Noise-Induced and Age-Related Hearing Loss in Humans and Animals: New Insights and Novel Therapies"**

DAY 2, SATURDAY, APRIL 29th

08H00-09H25 SESSION V

VESTIBULAR DISORDERS: VESTIBULAR IMPLANTS AND REGENERATIVE MEDECINE

Chairs : Yi-Chao Hsu, Yann Nguyen, Mohamed Amine El Alami

08h00–08h20 **Charles C. DELLA SANTINA**, Johns Hopkins School of Medicine, Baltimore, USA.
Title: **Vestibular Implantation and Long-Term, Continuously Motion-Modulated Stimulation to Treat Patients Disabled by Bilateral Vestibular Hypofunction**

08h20–08h40 **Nils GUINAND**, Clinical Neurosciences, University Hospital, Geneva, Switzerland.
Title: **The Cochleo-Vestibular Implant: Update and Remaining Challenges**

08h40–08h55 **Hanae LAHLOU**, Harvard Medical School, Mass Eye and Ear Infirmary, Boston, USA.
Restoration of Vestibular Function by Regeneration of Type I and Type II Hair Cells in Mature Mouse Utricle

08h55–09h10 **Ghizlene LAHLOU**, Institut de l'Audition, Institut Pasteur, AP-HP, Paris, France.
Title: **Assessing the Potential of Adeno-Associated Virus Serotypes to Target the Hair Cells of the Human Inner Ear for Gene Therapy**

09h10-09h25 **Kazusaku KAMIYA**, Juntendo University Faculty of Medicine, Tokyo, Japan.
Title: **AAV Gene Therapy and iPS Cell-Based Drug Development Targeting Cochlear Gap Junction**

09H25- 10H10 COCHLEAR SYMPOSIUM

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10H10-11H00 COFFEE BREAK (POSTERS VISIT)

11H00-12H30 SESSION VI

THERAPY 1 GENE THERAPY FOR DEAFNESS AND BALANCE DISORDERS

Chairs: Anne-Lise Giraud, Zheng-Yi Chen, Razika Bencheikh

11h00–11h20 **Christine PETIT**, Institut de l'Audition, Institut Pasteur, Paris, France.
Title: **Sensorineural Deafness: From Genetic Architecture to Gene Therapy**

11h20–11h50 **Federico MINGOZZI**, Chief Science &Technology Officer, Spark Therapeutics, Philadelphia, USA.
Title: **Progress and Challenges in the Development of *In Vivo* Gene Therapies with AAV Vectors**

11h50– 12h10 **Vincent VAN ROMPAEY**, University of Antwerp–Antwerp University Hospital, Antwerp, Belgium.
Title: **Disease-Modifying Therapy for Autosomal Dominant Hereditary Hearing Loss in DFNA9**

12h10–12h30 **Hinrich STAECKER**, Department of Otolaryngology, Hannover Medical School, Hannover, Germany.
Title: **Gene Editing Rescues Hearing in the Shaker-1 Mouse Model of Usher Syndrome Type-1B**

12H30-14H00 LUNCH BREAK (POSTERS VISIT)

DAY 2, SATURDAY, APRIL 29th

14H00-15H25	SESSION VII

HEARING LOSS AND THERAPIES

Chairs: Didier Dulon, Mohamed Mahtar, Paul Avan

14h00–14h15 **Roni HAHN**, Department of Human Molecular Genetics Biochemistry, Faculty of Medicine Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel.
Title: **From Big Data to Gene Therapy–Precision Medicine for Deafness**

14h15–14h30 **Yi-Chao HSU**, Department of Audiology and Speech-Language Pathology, MacKay Medical College, Taipai, Taiwan.
Title: **Implantation of Neural Progenitor Cells Derived from Human Induced Pluripotent Stem Cells Improves Sensorineural Hearing Loss in Mouse Model**

14h30 –14h45 **Verena SCHEPER,** Department of Otorhinolaryngology, Hannover Medical School, Hannover, Germany.
Title: **Design, Manufacture and First Clinical Application of an Additively Manufactured Patient-Individualized Drug Releasing Round Window Niche Implant to Treat Idiopathic Sudden Sensorineural Hearing Loss**

14h45–15h25 **Gabriel CORFAS**, Kresge Hearing Research Institute, University of Michigan, USA.
Title: **Hidden Hearing Loss: Pathogenic Mechanisms and Potential Therapeutic Approaches**

15H25-16H15	SESSION VIII

HEARING AIDS FOR SEVERE DEAFNESS, CHALLENGES AND LIMITATIONS

Chairs: Naima Deggouj, Haddou Ammar, Wade Chien

15h25–15h40 **Arnaud COEZ**, Sonova Audiological Care, Institut de l'audition, CERIAH, France.
Title: **Challenges for Conventional Hearing Aids in Severe Deafness**

15h40–15h55 **Lionel VANDERKERKEN**, Cliniques Universitaires Saint-Luc, Brussels**,** Belgium.
Title: **Hearing Care for Severe to Profound Hearing Losses. Hearing Aids, Cochlear Implants, Bimodal Hearing: a Short Review**

15h55–16h15 **Bernard FRAYSSE**, CHU Toulouse, Toulouse, France.
Title: **Prognostic Factors of Hearing Aids Outcomes: A Big Data Analysis**

16H15-17H00 COFFEE BREAK (POSTERS VISIT)

17H00-18H05	SESSION IX

COCHLEAR IMPLANTATION: CHALLENGES AND PERSPECTIVES

Chairs: Leila Essakali, Bernard Fraysse, Vincent Van Rompaey

17h00–17h20 **Shin-Ichi USAMI**, Shinshu University School of Medicine, Nagano, Japan.
Title: **Could the Genetic Origin of Sensorineural Hearing Loss Affect the Outcomes of Cochlear Implantation?**

17h20–17h35 **Fouad BENARIBA**, Hopital Militaire d'Instruction Mohammed V, Rabat, Morocco.
Title: **Challenges in Cochlear Implantation in Inner Ear Malformations**

17h35–17h50 **Thierry MOM**, Centre Hospitalier Universitaire Clermont-Ferrand, France.
Title: **Management of Difficult Cases in Cochlear Implantation: from Anticipation to Achievement**

17h50–18h05 **Razika BENCHEIKH**, Hôpital des spécialités, CHU Avicenne, Rabat, Morocco.
Title: **Cochlear Implantation in Malformed Cochlea: Experience of ENT-HNS University Hospital Rabat**

20H00	SYMPOSIUM DINNER

DAY 3, SUNDAY 30th, APRIL , 2023

08H00-09H40	SESSION X

THERAPY 2 NEXT GENERATION GENE THERAPY FOR DEAFNESS

Chairs: Saaid Safieddine, Mohamed Ridal, Hinrich Staecker

08h00–08h20 **Jeffrey HOLT**, Harvard Medical School, Mass Eye and Ear Infirmary, Boston, USA.
Title: **Function, Dysfunction and Restoration of Sensory Transduction Channels in Auditory Hair Cells**

08h20–08h40 **Zheng-Yi CHEN**, Harvard Medical School, Mass Eye and Ear Infirmary, Boston, USA.
Title: **Treatment of Autosomal Dominant Hearing Loss By In Vivo Delivery of Genome Editing Agents**

08h40–09h05 **Erwin VAN WYK**, Radboud University Medical Center, Nijmegen, Netherlands.
Title: **RNA Therapies for Otogenetic Disorders: Current Status**

09h05–09h25 **Wade CHIEN**, Johns Hopkins School of Medicine, Baltimore, USA.
Title: **Combined AAV-Mediated Gene Replacement Therapy Improves Auditory Function in a Mouse Model of Human DFNB42 Deafness**

09h25–09h40 **Najate BENAMER**, Institut de l'Audition, Institut Pasteur, Paris, France.
Title: **Dual AAV-Mediated Gene Augmentation Therapy Restores Hearing in Auditory Synaptopathy Mouse Model**

09H40-10H25	SENSORION SYMPOSIUM

10H25-11H00	COFFEE BREAK

11H00-11H40	SESSION XI
ROBOTIC SURGERY	
Chairs: Wade Chien, Aziz El Amraoui, Fahd Elayoubi	

11h00–11h20 **Yann NGUYEN**, Institut de l'Audition, Institut Pasteur, AP-HP, Paris, France.
Title: **Robot-Based Cochlear Implant Insertion**

11h20–11h40 **Vedat TOPSAKAL**, Hôpital UZ Brussel, Jette, Belgium.
Title: **Robotic Assisted Cochlear Implantation: the Belgian Clinical Experience with the Hearo procedure**

11H40-13H00	ROUND TABLE
WHAT STEPS CAN BE TAKEN TO STRENGTHEN THE TRANSLATIONAL APPROACH IN INNER EAR THERAPY RESEARCH?	

CLOSING REMARK AND POSTER PRIZE CEREMONY

13H00-14H30	LUNCH & FAREWELL

DAY 3, SUNDAY 30th, APRIL

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POSTER TITLE LIST

POSTERS ON TV1

P1. Evaluation of hearing and quality of life in patients implanted with a bone-anchored hearing aid

Zainab Benyahia[1], Kawtar Ayyad[1], Bencheikh Razika[1], Anas Benbouzid[1],Abdelilah Oujilal[1], and Essakalli Leila[1]

[1]University Hospital IBN SINA - Rabat – Morocco

P2. Outcomes of late cochlear implantations in prelingual deafened children

Dounia Berrada El Azizi[1], Mohamed Amine Ait Elhadj[1], Sara Rochd[1], YoussefLakhdar[1], Othmane Benhoummad[2], Youssef Rochdi[1], and Abdelaziz Raji[1]

[1]Mohammed VI university hospital, ENT-HNS department, Marrakech – Morocco

[2]University hospital, ENT-HNS department, Agadir – Morocco

P3. Functional outcomes in cochleostomy and round window insertion technique of the cochlear implantation

Driss El Idrissi[1], Ayoub Zantaoui[1], Youssef Lakhdar[1], Othmane Benhoummad[2],Youssef Rochdi[1], and Abdelaziz Raji[1]

[1]Mohammed VI university hospital, ENT-HNS department, Marrakech – Morocco

[2]University hospital, ENT-HNS department, Agadir – Morocco

P4. Benefits of Cochlear implantation in children with multiple handicap and comorbidities: evaluation and parents' satisfaction

Laila Liqali[1], Hafsa Agouassif[1], Youssef Lakhdar[1], Othmane Benhoummad[2], Youssef Rochdi[1], and Abdelaziz Raji[1]

[1]Mohammed VI university hospital, ENT-HNS department, Marrakech – Morocco

[2]University hospital, ENT-HNS department, Agadir – Morocco

P5. Quality of life in prelingually-deafened, late-implanted patients

Fatima Ezzahra Rizkou[1], Salma Salhi[1], Youssef Lakhdar[1], Othmane Benhoummad[2],Youssef Rochdi[1], and Abdelaziz Raji[1]

[1]Mohammed VI university hospital, ENT-HNS department, Marrakech – Morocco

[2]University hospital, ENT-HNS department, Agadir – Morocco

P6. Evaluation of the functional results of cochlear implantation at the University Hospital Of Marrakech

Zineb Sarda[1], Youssef Lakhdar[1], Othmane Benhoummad[2], Youssef Rochdi[1], and Abdelaziz Raji[1]

[1]Mohammed VI university hospital, ENT-HNS department, Marrakech – Morocco

[2]University hospital, ENT-HNS department, Agadir – Morocco

P7. Impact of number and integrity of inserted electrodes in the cochlea on speech performance of pediatric cochlear implantation

Mohammed Rami[1], Youssef El Khalifa[1], Mohamed Amine Aitlhadj[1], Youssef Lakhdar[1], Othman Benhoummad[2], Youssef Rochdi[1], and Abdelaziz Raji[1]

[1]Mohammed VI university hospital, ENT-HNS department, Marrakech – Morocco

[2]University hospital, ENT-HNS department, Agadir – Morocco

P8. Complications of cochlear implant surgery

Ichtiyak Amou[1], Samia Kabbaj[1], Youssef Lakhdar[1], Othmane Benhoummad[2], Youssef Rochdi[1], and Abdelaziz Raji[1]

[1]Mohammed VI university hospital, ENT-HNS department, Marrakech – Morocco

[2]University hospital, ENT-HNS department, Agadir – Morocco

POSTERS ON TV2

P9. Limits of cochlear implantation in inner ear malformations

Hafsa Agouassif[1], Soufiyane Kajai[1], Youssef Lakhdar[1], Othmane Benhoummad[2], Youssef Rochdi[1], and Abdelaziz Raji[1]

[1]Mohammed VI university hospital, ENT-HNS department, Marrakech – Morocco

[2]University hospital, ENT-HNS department, Agadir – Morocco

P10. Cochlear Implantation in patient with Dandy-walker Syndrome

Abdelilah Arioua[1] and Salma El Alaoui El Rhoul[1]

[1]University Hospital Hassan II – Morocco

P11. Cochlear implantation in children with Effusion otitis media

Soufiyane Kajai[1], Atmane Zaroual[1], Youssef El Khalifa[1], Youssef Lakhdar[1], Othmane Benhoummad[2], Youssef Rochdi[1], and Abdelaziz Raji[1]

[1]Mohammed VI university hospital, ENT-HNS department, Marrakech – Morocco

[2]University hospital, ENT-HNS department, Agadir – Morocco

P12. Challenges of cochlear implantation in inner ear malformations

Youssef El Khalifa[1], Aitlhadj Mohamed Amine[1], Youssef Lakhdar[1], OthmaneBenhoummad[2], Youssef Rochdi[1], and Abdelaziz Raji[1]

[1]Mohammed VI university hospital, ENT-HNS department, Marrakech – Morocco

[2]University hospital, ENT-HNS department, Agadir – Morocco

P13. Cochlear reimplantation: surgical technique and results

Malak Moufannane[1], Ayoub Zantaoui[1], Youssef Lakhdar[1], Othmane Benhoummad[2], Youssef Rochdi[1], and Abdelaziz Raji[1]

[1]Mohammed VI university hospital, ENT-HNS department, Marrakech – Morocco

[2]University hospital, ENT-HNS department, Agadir – Morocco

P14. Cochlear implantation for neurosensory hearing loss: experience of the ENT department at the Mohammed VI Hospital University of Oujda

Naoufal Ramdani[1], Abdelilah Rguiyg[1], Drissia Benfadil[1], Azeddine Lachkar[1], andFahd Elayoubi[1]
1Mohammed VI University Hospital [Oujda] – Morocco

P15. Predicting round window accessibility during cochlear implant surgery based on pre-operative imaging of the temporal bone

Salah Youbi[1], Atmane Zaroual[1], Youssef Lakhdar[1], Othmane Benhoummad[2], Youssef Rochdi[1], and Abdelaziz Raji[1]
[1]Mohammed VI university hospital, ENT-HNS department, Marrakech – Morocco
[2]University hospital, ENT-HNS department, Agadir – Morocco

P16. Cochlear implantation in post-meningitis deafness

Atmane Zaroual[1], Soufiane Kajai[1], Youssef Elkhalifa[1], Youssef Lakhdar[1], YoussefRochdi[1] , and Abdelaziz Raji[1]
[1]Mohammed VI university hospital, ENT-HNS department, Marrakech – Morocco

P17. Post-Meningitis Deafness: Experience of the ENT Department at HSR (2019-2021)

Zineb Berdi[1], Mohammed Azeddine[1], Razika Bencheikh[1], Mohammed Anas Benbouzid[1], Abdelillah Oujilal[1], and Leila Essakalli[1]
[1]ENT -Neck Surgery Department. Specialties Hospital. Ibn Sina University Medical Center.Mohammed V University. Rabat – Morocco

P18. Hearing aids in flight personnel

Mohammed Elakhiri*[1], Benchafai Ilyas [1], Chabraoui Youness [1], Aljalil Abdelfatah [1], Ammar Hadou [1], and Darouassi Youssef[1]
[1]ENT Département Avicenne military hospital, Marrakech, Morocco

POSTERS ON TV3

P19. Gene therapy for hearing loss: a systematic review

Frederic Acke [1,2,3], Charlotte Defrancq[1], Bart Leroy[4,5], Ingeborg Dhooge[1], and Zheng-Yi Chen[2,3]
[1]Department of Otorhinolaryngology, Ghent University and Ghent University Hospital, Ghent, Belgium - Belgium
[2]Eaton Peabody Laboratory, Massachusetts Eye and Ear, Boston, MA, USA - United States
[3]Department of Otolaryngology and Program in Neuroscience, Harvard Medical School, Boston, MA ,USA - United States
[4]Department of Ophthalmology, Ghent University and Ghent University Hospital, Ghent, Belgium - Belgium
[5]Division of Ophthalmology and Center for Cellular Molecular Therapeutics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA- United States

P20. Design and validation of mutant allele-specific antisense oligonucleotides for the future treatment of adult-onset hearing loss type DFNA9

Erik De Vrieze[1], Ronald Pennings[1], Hannie Kremer[1], and Erwin Van Wijk[1]
[1]Radboud University Medical Center [Nijmegen] – Netherlands

P21. Engineering Efferent Feedback to Protect Hearing

Yuanyuan Zhang[1], Hakim Hiel[2], Philippe Vincent [2], Megan Beers-Wood[2], Ana Belen Elgoyhen[3], Wade Chien[4], and Paul Fuchs[2]

[1]Renmin Hospital of Wuhan University - China
[2]Johns Hopkins University School of Medicine - United States
[3]Consejo Nacional de Investigaciones Científicas y Técnicas. - Argentina
[4]National Institutes of Health - United States

P22. CRISPR-Cas9 In Vivo Gene Editing of Otof in postnatal Mouse Auditory Hair Cells

Jean-Christophe Leclere[1], Yohan Bouleau[2], and Didier Dulon[3]

[1]Department of Head and Neck Surgery, Brest University Hospital, Brest, France - Brest University Hospital -France
[2]University of Bordeaux - University of Bordeaux - France
[3]Institut de l'Audition, INSERM UA06 University of Bordeaux - Institut de l'Audition, Institut Pasteur – France

P23. Dual vector gene therapy for DFNB16 hearing Loss

Olga Shubina-Oleinik[1], Carl Nist-Lund[1], Karl R. Koehler[1], and Jeffrey Holt[1]

[1]Boston Children's Hospital and Harvard Medical School - United States

P24. Developing digital biomarkers for auditory and vestibular Phenotyping in clinical trials

Erin Robertson-Dick[1], Jacek Urbanek[1], Rolando Acosta[1], Emily Redington[1], and Meghan Drummond[1]

[1]Regeneron – United States

P25. Developing From Big Data to Gene Therapy - Precision Medicine for Deafness

Roni Hahn*[1], Lara Kamal[1], Zippora Brownstein[1], Tal Koffer-Brill[1], Shahar Taiber[1],Yazeed Zoabi[2], Noam Shomron[2], Rachel Katz[3], Tal Patalon[3], and Karen Avraham[1]

[1]Department of Human Molecular Genetics Biochemistry, Faculty of Medicine Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel
[2]Department of Cell Developmental Biology, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Maccabi Healthcare Services, KSM-Kahn-Sagol-Maccabi Research, and Innovation Center, Tel Aviv, Israel

POSTERS ON TV4

P26. GJB2 and LRTOMT variants associated with non-syndromic deafness in mauritanian families

Malak Salami[1], Crystel Bonnet[2], Selma Mohamed Brahim[3], Ely Cheikh Mohamed Moctar[4], Abdallahi Dedy[5], Ledour Abdel Vetah[6], Fatimetou Veten[7], Cheikh Tijani Hamed[8], Christine Petit[9], and Ahmed Houmeida[10]

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Es-Sddik El Bakri[1], Othmane Lamoihi[1], Lakhder Youssef[1], Othman Benhoummad[2], Youssef Rochdi[1], and Abdelaziz Raji[1]

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Abdeljabbar Moussaoui[1], Kawtar Cherrabi[1], Mohamed Mehdi El Fakiri[1], and Othmane Benhoummad[1]

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Hamza Benjelloun[1], Mohamed Yafi[1], Youssef Lakhdar[1], Othmane Benhoummad[2], Youssef Rochdi[1], and Abdelaziz Raji[1]

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Youssef Darouassi[1], Iliass Benchafai[1] , Mohamed El-akhiri[1] , Mossab Tayane[1], Youness Chebraoui[1] , Mohamed Amine Hanine[1] , Amine Ennouali[1] , Abdelfettah Aljalil[1] , MohamedMliha Touati[1] , and Haddou Ammar[1]

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Ahmed salem Tvagha[1], Rguyeg Abdelilah[1], Mouna Baddi[1], Drissia Benfadil[1],Azeddine Lachkar[1], and Fahd Elayoubi[1]

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P66. Classification of inner ear malformations

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Mohamed Amine Aitlhadj[1], Mohamed Rami[1], Lakhder Youssef[1], Othmane Benhoummad[2], Youssef Rochdi[1], and Abdelaziz Raji[1]

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P69. Predictable sequential structure enhances auditory sensitivity

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P70. Study of hearing loss in pilots

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PLENARY SESSION ABSTRACT

Eligibility to gene therapy: the issue of quantitative assessment of auditory sensory cells and neurons

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Abstract

The outcome of future gene therapies in human adults may be limited once the architecture of the auditory system is modified beyond repair by a degenerative process. This calls, not only for early screening including systematized genetic investigations, but also for objective assays allowing the number, location and functionality of essential auditory elements to be established. In theory, outer hair cells and low-threshold auditory neurons can be selectively probed, using otoacoustic emissions (OAEs) and electrocochleography (Ecog) respectively. The lack of consensual method for extracting estimations of cell survival and of indispensable complex parameters, such as tectorial membrane coupling and stereocilia cohesion, will be discussed. As for inner hair cells and subgroups of auditory neurons, no direct noninvasive method can be said to reliably evaluate their status, hence the acknowledged existence of 'hidden' hearing losses. A similar issue is raised in cochlear implantees in whom the achieved performance, sometimes stunningly good and sometimes indifferent, partly depending on auditory-neuron survival, can hardly be predicted better than in hindsight. Thus significant efforts are still needed to determine the minimum set of data allowing rational clinical trials of gene therapy to be programmed with a reasonable chance of success.

Keywords: otoacoustic emissions, electroochleography, audiology

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New technologies in medical genetics for early hearing loss: advances and obstacles

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Abstract

The proportion of genetic prelingual sensorineural hearing impairment is currently estimated at 2/3. The knowledge about nonsyndromic hearing loss has tremendously increased since 1995 and more than 120 genes have been cloned. In the same time, several hundred syndromic associations have been described in which the hearing deficit may be associated with abnormalities or malformations in other organs. The development of routine molecular diagnosis has allowed the identification of a genetic cause in a large part of sporadic hearing losses previously classified as "unknown cause". Currently, genetic consultations and investigations are recommended in the management of childhood hearing loss.
Regarding the molecular diagnosis, targeted molecular analysis are still proposed in some cases for the more frequently implicated genes. However, the great genetic heterogeneity of prelingual hearing impairments makes it very interesting to use a recent high throughput sequencing (NGS: Next Generation Sequencing) technology to simultaneously analyze a large number of genes.
We will present the medical genetics strategy used in our Reference Centre for Genetic hearing loss to date and we will illustrated with some cases the improvement but also the remaining difficulties in genetic diagnosis of early hearing impairments.

Keywords: Genetics

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Background Check: Using the Mouse to Elaborate on the Genetics of Mammalian Hearing

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Abstract

Background

The similarities between human and mouse auditory structure and function, and the concordance between orthologous genes critical for hearing function, has seen the mouse become the predominant model organism for: elaborating upon the genetic landscape of mammalian hearing; interrogating the pathophysiology associated with gene mutations; and, establishing the efficacy of therapeutic interventions to protect and/or restore hearing. However, the findings of large-scale mouse mutant screens indicate we are still far from identifying all of the genes critical for mammalian auditory function.

Objectives

To investigate hearing loss and additional phenotypes of knockout mouse models in the presence and absence of *Cdh23ahl*, an allele common to several widely used inbred mouse strains.

Methods

Measure the hearing thresholds, and assess for additional phenotypes, exhibited by knockout mouse mutants maintained on a standard C57BL/6N background and compare these to the phenotypes they exhibit when maintained on a co-isogenic C57BL/6N background in which the *Cdh23ahl* allele has been 'repaired' using CRISPR/Cas9 (C57BL/6N.*Cdh23c.753A> G*).

Results

We have studied knockout mouse mutants for two members of the Basigin family of neural cell adhesion molecules, *Neuroplastin* and *Embigin*. We find their respective auditory phenotypes are more severe in the presence of the *Cdh23ahl* allele. For *Neuroplastin* this genetic interaction is explained due to an interaction with Plasma Membrane Calcium ATPases, but this is not the case for *Embigin*. Furthermore, absence of *Embigin* on a standard C57BL/6N

*Speaker

background leads to sub-viability, brain and cardiac defects, which are not observed on the 'repaired' co-isogenic C57BL/6N background.

Conclusions

Our findings highlight the importance of knowing, controlling and reporting the genetic background of mutant mouse lines. More importantly, our studies demonstrate an effect of the common *Cdh23ahl* allele outside of the cochlea, and the identification of brain defects has ramifications for our understanding of hearing loss mechanisms and potential therapeutic interventions.

Funding
Honorary MRC Senior Non-Clinical Fellowship (MR/X004597/1)

Genetic architecture of prelingual deafness in Saharan, sub-Saharan and Middle East populations

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Abstract

The majority of prelingual sensorineural hearing impairment (HI) cases are of genetic origin. These are monogenic disorders, genetically highly heterogeneous. For genetic counseling as well as in the perspective of gene therapy, it is essential that all patients have access to a molecular diagnosis. In numerous countries, the molecular diagnosis methods used will have to take into account the relative contribution of the various deafness genes and the existence of prevalent pathogenic variants. To this purpose, we are exploring here the variants responsible for deafness in a cohort of 450 unrelated patients affected by severe to profound early onset HI from Africa, in Saharan regions, Algeria, Morocco, Tunisia, and sub-Saharan region, Mauritania, and from Middle East, Jordan, countries. We developed a targeted exome high throughput sequencing of 157 known deafness genes (HearPanel-IdA). As a result, 378 patients carried biallelic prediected pathogenic variants in DFNB genes, 13 patients carried monoallelic variants in DFNA and ADSD genes, and one patient carried one variant in DFNX gene, thus ascertaining the molecular diagnosis for a total of 392/450 patients (87.1%). A total of 213 variants were identified in 49 different deafness genes, and 78 of these variants (36.7%) had not been reported previously. Remarkably, we found 63/450 patients (14%) with biallelic predicted pathogenic variants in Usher syndrome genes of which 40 of them (8.8%) were initially diagnosed and confirmed as Usher. This makes HearPanel-IdA a powerful and cost-effective tool to identify rare variants causing HI in populations with a high proportion of consanguineous marriages. The use of HearPanel-IdA as a routine investigation should not only facilitate the detection of rare variants in uncommon HI genes, but also contribute significantly to the early diagnosis of specific forms of syndromic HI such as Usher syndrome, for which early cochlear implantation is of utmost importance because of the secondary sight loss.

Keywords: hearing impairment, Usher syndrome, targeted, exome sequencing, pathogenic variants

*Speaker

The frequency of the GJB2 c.35delG mutation in patient with non-syndromic hearing loss : First series of Mohammed VI University Hospital of Marrakech.

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Abstract

Background: Hereditary hearing loss can be classified into syndromic and non syndromic hearing loss. Syndromic hearing loss includes more than 400 syndromes in which hearing loss occurs in addition to other signs and symptoms. Non Syndromic Hearing Loss (NSHL) can be inherited in an autosomal recessive manner (75–80%), autosomal dominant pattern (20–25%) or in rare instances as an X linked or mitochondrial pattern of inheritance (1–2%). In cases of (NSHL) , the most common mutation occurs in the Gap Junction Beta 2 gene (GJB2) which can account for up to 50% of autosomal recessive non syndromic hearing loss cases (ARNSHL), and for 15–30% of sporadic cases. The GJB2 gene encodes connexin 26 which is a gap junction protein. This protein allows passage of potassium ions in the inner ear. More than 110 different mutations have been identified out of which the 35delG mutation is the most frequent in the majority of people and accounts for 70% of all GJB2 mutations. Phenotypic variations in patients with the GJB2 mutation can be considerable. The degree of hearing loss also varies and it can be mild to severe.
The objective of our study is to determine the prevalence of the 35delG mutation in non-syndromic autosomal-recessive cases and sporadic cases recruited at the Mohammed VI University Hospital of Marrakech.

Patients and methods: The study was conducted on 93 non related Moroccan probands affected by congenital non syndromic sensorineural hearing impairment, ranging from mild to profound forms. We looked for the 35delG the mutation by Sanger sequencing.

Results : We will report the frequency of the 35delG mutation in non-syndromic autosomal-recessive cases and sporadic cases
Conclusion: The systematic screening of the 35delG in the GJB2 gene, should facilitate routinely used diagnostic for genetic counselling in Morocco. Patients with a GJB2 mutation show an excellent outcome with cochlear implants, thus reiterating the importance of genetic testing for children with non-syndromic hearing loss.

Keywords: Non syndromic hereditary hearing loss, GJB2 c.35delG mutation, Mohammed VI University Hospital of Marrakech

*Speaker

Data Science in Hearing Research

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Abstract

We present our research where we have repurposed hearing health data from UCLH for research. We will show how this data can be standardised and linked across datasets to create a multimodal data resource. Finally, we will demonstrate some of the applications of this resource.

*Speaker

Candidacy for cochlear implantation in prelingual profoundly deaf adult patients

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Isabelle Mosnier1,2, Hannah Daoudi1,2, Evelyne Ferrary1,2, Yann Nguyen1,2, Olivier Sterkers1,2, Ghizlene Lahlou1,2

Abstract

Cochlear implantation is usually not recommended for prelin-gually profoundly deaf adults, although some of these patients might benefit from it. This study aimed to define the candidates for cochlear implantation in this population. This ret-rospective study reviewed 34 prelingual profoundly deaf patients who had received a cochlear implant at 32±1.7 years old (16-55), with at least 1 year of follow-up. Speech perception and quality of life were assessed before and 3, 6, 12 months after cochlear implantation, then ev-ery year thereafter. According to the words speech intelligibility in quiet (WSI) 1-year after implantation, 2 groups were identified: good performer (GP) with WSI ≥50% (n=15), and poor performer (PP) with WSI ≤40% (n=19). At 1-year, mean WSI improved by 28±4.6%(-20–100) ($p < 0.0001$). In GP, intelligibility for words and sentences, communication and quality of life scales improved. In PP, communication scale improved, but not auditory performance nor quality of life. GP and PP differed pre-operatively in speech production, communication abilities, and WSI in best-aided conditions. In prelingually profoundly deaf adults, a dramatic auditory performance benefit could be expected after cochlear implanta-tion if the patients have some degree of speech intelligibility in aided conditions and have developed oral communication and speech production.

*Speaker

Effect of Radiological Grade of Cochlear Ossification on Cochlear Implant Outcome in Post meningitis Deafness

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Abstract

Objectives: Cochlear implantation provides significant benefits to patients with post meningitis deafness; however, the prediction of the outcome is difficult. Therefore, the goal was to investigate whether there is a correlation between cochlear implantation outcome in post meningitis deafness and the radiological grade of cochlear ossification.
Methods: In this retrospective cohort study conducted at King Abdulaziz University Hospital, Riyadh, Saudi Arabia, between January 2013 and December 2017, nine patients with 14 diseased ears were included. All patients with post meningitis deafness who had cochlear ossification and underwent cochlear implantation were included. Patients' demographic data and postoperative audiological outcome were recorded. Preoperative computed tomography (CT) and magnetic resonance imaging (MRI) findings were independently reviewed by two neuroradiologists and graded for cochlear ossification. The correlation between the preoperative radiological grade of cochlear ossification and post cochlear implant audiological outcome was examined.

Results: The mean duration of deafness before implantation was 6.5 months, and the average PTA4k for all included ears was 28.9 dB. The average speech reception threshold was 22.5 dB. There was no significant difference in the audiological outcome between the different radiological degrees of cochlear ossification using either MRI or CT.
Conclusion: The present study showed that the radiological degree of cochlear ossification post meningitis is not a useful predictor of the audiological outcome post cochlear implant. However, the small sample size remains a major limitation of the current study.

*Speaker

Evaluation of the Post-Implant Cochlear Fibrotic Reaction

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Abstract

Background : Cochlear implant is the method of choice for the rehabilitation of severe to profound sensorineural hearing loss. The study of the tissue response to cochlear implantation and the prevention of post-cochlear-implant damages are areas of interest in hearing protection research.
Objective : The objective was to assess the efficacy of dexamethasone-eluting electrode array on endo canal fibrosis formation by three-dimensional immunofluorescence analysis in implanted Mongolian gerbil cochlea.

Methods : Two trials were conducted after surgery using Mongolian gerbil implanted with dexamethasoneeluting or non-eluting intracochlear electrode arrays. The animals were then euthanised 10 weeks after implantation. The cochleae were prepared (electrode array in place) according to a 29-day protocol with immunofluorescent labelling and tissue clearing. The acquisition was carried out using light-sheet microscopy. Imaris software was then used for three-dimensional analysis of the cochleae and quantification of the fibrotic volume.
Conclusion : The analysis of 12 cochleae showed a significantly different mean volume of fibrosis (2.16 x 108 μm3 +/- 0.15 in the dexamethasone eluting group versus 3.17 x 108 μm3 +/- 0.54 in the non-eluting group) (p = 0.004). The cochlear implant used as a corticosteroid delivery system appears to be an encouraging device for the protection of the inner ear against fibrosis induced by implantation. Three-dimensional analysis of the cochlea by light-sheet microscopy was suitable for studying post-implantation tissue damage.

Keywords: auditory implant, dexamethasone, hearing loss, rehabilitation, clearing, imaging, light, sheet microscopy

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Day Surgery for Cochlear Implantation under Conscious Sedation with Same-Day Fitting

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Abstract

Objectives: To evaluate the feasibility of performing cochlear implantation under conscious sedation (CS) as day surgery with same-day fitting.

Materials and methods: All patients underwent cochlear implantation under CS between November 2017 and April 2018. The data collected included demographic information, preoperative clinical characteristics, surgical details, postoperative fitting information, and side effects, if any.

Results: Nine patients had 11 cochlear implants (CIs) placed under CS (2 patients received bilateral CIs). One patient's data were excluded from the audiological results because conversion to general anesthesia (GA) was necessary. One patient (11%) vomited just before the end of the procedure. Seven patients had uneventful procedures. Eight (88%) patients were discharged home the same day. There was a statistically significant difference in recovery time between the CS group and the GA group ($t=-2.26$, $df=12$, $p< 0.05$). In the CS group, there was no statistically significant change in the maximum comfortable loudness level for all electrodes from the day of the surgery to the following day. However, there was a statistically significant difference in the threshold levels of all electrodes from the day of the surgery to the following day ($Z=-2.04$, $N=120$, $p< 0.05$). Further analysis revealed a statistically significant difference in the four most apical electrodes ($Z=-3.496$, $N=40$, $p< 0.0001$), but not in the middle or basal electrodes.

Conclusion: Cochlear implantation can be performed under CS with careful patient selection. This approach facilitates same-day fitting and day surgery by minimizing comorbidity.

*Speaker

Post meningitis hearing loss: from screening to hearing rehabilitation

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Abstract

Background : Sensorineural hearing loss (SNHL) is one of the most frequent and devastating sequelae of bacterial meningitis.

Objective: To evaluate the effect of bacterial meningitis on hearing, to analyze risk factors for post-meningitic deafness in the pediatric population, to evaluate outcomes and challenges of the different treatments, and to demonstrate the importance of close audiological follow up in this group of patients.

Materials and methods: We reviewed audiological screening and follow-up data of 379 children treated for acute bacterial meningitis from January 2017 to December 2022. We have carried out audiological assessment and speech therapy follow-up and the evaluation of patients who have undergone hearing rehabilitation with cochlear implants or hearing aids.

Results: based on the screening protocol, using age-appropriate hearing tests, diagnosis of post-meningitis deafness was suspected in **34.1%**, which has been confirmed by auditory brainstem responses (ABR) and auditory study state response (ASSR) in the cases of severe and profound hearing loss. Mean age was **5.4** years old ranging from **6** months to **14** years old. Main causative pathogens were *S. pneumoniae* (**44.4%**) and *N. meningitidis* (**21.1%**). Children with mild to severe and unilateral profound sensorineural deafness were managed with conventional hearing aids and received audiological follow up. Children with severe to profound bilateral sensorineural hearing loss (**12 cases**) were further evaluated for cochlear implantation according to our preoperative assessment protocol, **11** cases have been implanted and **1** case is undergoing a pre-implant assessment. Cochlear ossification has been encountered intraoperatively in **9** patients, **5** of which had evidence of decreased cochlear patency on the pre-operative CT scan. However, it was missed by CT in the remaining **3** cases and only identified by MRI. Surgical management consisted of drilling a tunnel through the bony obstruction into the scala tympani of the basal turn to expose an adequate lumen to permit safe electrode insertion. Complete electrode insertion was achieved in **8** cases, the **3** others has had partial electrode insertion confirmed on post-operative Stenver's view X-ray. No post-operative complication has been noted and all patients received speech therapy

*Speaker

and close follow-up after hospital discharge. The evaluation using APCEI score has been about 15.1 on average ranging from 13 to 18, in this group of patients (average delay of 26.76 months). Post cochlear implantation hearing threshold has been variable with a mean threshold of 50 decibels. Mean APCEI score has been about 15.5 in complete insertion of the electrode compared to incomplete insertion (13.6). We have found no difference in APCEI score between round window or cochleostomy electrodes insertion.
Conclusion: Post-meningitis hearing loss can occur immediately or several months or years after acute bacterial meningitis. Therefore, careful audiologic evaluation and follow-up is essential for diagnosis and appropriate management. Patients with severe to profound sensorineural post-meningitis hearing loss should be referred quickly for cochlear implantation candidacy evaluation before onset of extensive fibrosis and ossification.

Extracellular Vesicles in Inner Ear Therapies-Pathophysiological, Manufacturing, and Clinical Considerations

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Abstract

Novel therapeutics such as extracellular vesicles (EVs) could provide a means to modulate inflammation, stress pathways and apoptosis in the inner ear. Thus, EVs may become the most promising next generation therapeutic in neurotology. Preclinical results on the efficacy of EVs in the inner ear will be presented. Possible indications for the use EVs such as protection of spiral ganglion neurons, immunomodulation and activation of endogenous progenitor cells or even treatment of Meniere's disease will be discussed. The challenges associated with toxicity, biodistribution and manufacturing of EVs under GMP conditions to allow for their application in the human inner ear will be presented. Manufacturing and regulatory issues that need to be addressed to develop EVs as a biological product for their use in the inner ear are outlined. Finally, first in man application as proof of concept will be presented.

*Speaker

Perilymph diagnostics: A new possibility for the development of precision treatment?

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Cluster of Excellence Hearing4all

Abstract

Introduction: Analysis of human perilymph has been shown to be a feasible method for gaining information about the individual protein composition of the human perilymph. Mass spectrometry was utilized to detect the individual protein profile of human perilymph collected during cochlear implantation from patients with severe hearing loss. The proteins were identified using the shot-gun proteomics method and quantified and analysed using Max Quant, Perseus and IPA software. Proteome profiles were correlated to clinical data. Molecular inner ear profiles that may be able to predict clinical performance were identified in patients with excellent and poor speech performance. Stratification of patients according to their underlying disease causing hearing loss, we were able to identify putative disease marker. In addition, a human atlas of proteins was generated based on individual proteome profiles. Thus, perilymph analysis may open up new possibilities for patient characterisation and stratification prior to cochlear implantation. The impact of such prediction algorithms on diagnosis and treatment needs to be established in further studies.

*Speaker

Human Inner Ear Organoids: A New Tool to Probe Hearing Restoration Therapeutics

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Abstract

Human induced Pluripotent stem cells (hiPSCs) directed to differentiate into Inner Ear Organoids (IEOs) recapitulate several aspects of inner ear morphogenesis *in vitro*. These systems represent unique tools to complement and refine our understanding of human otic differentiation, model developmental defects and to validate therapeutic strategies.

We have characterized IEOs generated from different human iPSC lines by multiplexed immunostaining and single-cell RNA sequencing, providing a signature of *in vitro* derived otic -placode, -epithelium, -neuroblasts, and -sensory epithelia. Further, we have benchmarked these tissues to different stages of human otic development, from embryonic week 4 to fetal week 12. The maturity of hair cells and supporting cells derived after 50-60 days of differentiation is equivalent to vestibular sensory epithelia at week 10 or cochlear tissue at week 12 of development, before functional onset. Together, our data indicate that the current state-of-the-art protocol enables the specification of *bona fide* otic tissue, supporting the application of IEOs to inform inner ear biology and disease.
We are now making use of these systems, in combination with CRISPR/Cas9 editing, to model a novel genetic mutation recently identified in a Pendred syndrome patient and to assess its causative relation with hearing loss. Finally, we are exploiting IEOs to assess different AAV vector tropisms and to optimize expression cassettes with the aim to develop specific targeting strategies for hearing restoration.

*Speaker

Ebselen (SPI-1005) Treatment Improves Hearing Loss and Speech Discrimination in Meniere's Disease

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Abstract

Background: SPI-1005 contains an investigational new drug ebselen (novel anti-inflammatory) that was tested in a Phase2b RCT in definite Meniere's Disease (MD), where hearing loss, tinnitus, and vertigo were active. Improvements in low-frequency hearing, speech discrimination, and tinnitus were clinically relevant or statistically significant in ebselen vs placebo groups. This post-hoc analysis focused on affected ears and the correlation between hearing loss and speech discrimination across treatment groups overtime.
Methods: Randomized, double-blind, prospective, placebo-controlled, multicenter Phase2b (N=126) in adults (18-75) with definite MD. Patients were randomized to SPI-1005 (200 or 400mg BID) or placebo (1:1:1). Outcome variables were hearing thresholds (250-8000Hz), and Words-in-Noise (WIN) scores (0-35) in the affected ears over time (Baseline, Day28 and Day56). ANOVA was used to compare differences between groups over time. Pearson's correlation coefficient was calculated with hearing loss and speech discrimination as variables overtime.

Results: In the affected ears (baseline low-frequency hearing thresholds $\geq$30dB at 250, 500, or 1000Hz), the 400mg BID group (N=57) showed both clinically relevant and statistically significant improvements of 4.3$\pm$10.34dB (p-value=0.003) and WIN of 2.9$\pm$4.68 words (p-value$<$ 0.001) at Day56 from baseline. The placebo group (N=57) showed non-significant improvements of 1.6 $\pm$ 8.03dB (p-value=0.393) and 0.8 $\pm$ 4.94 words (p-value=0.203), respectively. The differences in WIN between the 400mg BID group and placebo were significant (p-value = 0.024), while the differences in low-frequency hearing were non-significant (p-value=0.126). Pearson' coefficient was inversely correlated (r= -0.83977, -0.81175, -0.83501 at Baseline, Day28 and Day56, respectively).
Conclusions: 4-weeks of SPI-1005 treatment resulted in improvements in low-frequency hearing that correlated with clinically relevant and statistically significant improvements in speech discrimination over an 8-week follow-up. The 400mg BID group showed the most durable auditory improvements at Day56 when compared to placebo. These findings influenced the study design and statistical analysis plan of the ongoing Phase3 RCT in Meniere's disease.

Keywords: hearing loss, tinnitus, meniere's disease, ebselen, SPI, 1005, clinical trial

*Speaker

Fluoroscopy guided cochlear implantation and robotized : Optimized control of electrode -array insertion

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Abstract

Background

Cochlear implantation is a well-codified surgical procedure. All steps are perfectly visually controlled during surgery but one: the electrode-array (EA) insertion. The quality of EA insertion totally relies on the haptic feedback of the surgeon, with mishappens occurring even in experienced hands. Translocation, basal kinks, or EA tip fold-overs have been reported by all teams. In addition, the quality of EA insertion could be increased by using a robotized arm.

Objectives

We aimed to improve EA-insertion by using fluoroscopy and robotized EA-insertion and check the advantage of this technique.

Methods

During one year, all candidates to cochlear implantation were operated on under fluoroscopy, any times the fluoroscopy dedicated room (Imabloc) was available, using the RobotOl® , robot dedicated to otologic surgery allowing a robotized EA-insertion at low speed.

Conclusions: 23 patients (10 women, 61+/-19 y.o.) were implanted in the Imabloc. 19 (82.6%) cases had a successful robotized EA-insertion with fluoroscopy control. All cases were implanted through the round window with a good EA - location within the scala tympani. However other cases failed and required classic manual insertion, either because of cochlear fibrosis, lack of mastoid room for adequately placing the RobotOl® , poor control of the fluoroscopy robotized C-arm or insufficient remote surgical control of the RobOtol®.

*Speaker

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Electrocochleography in cochlear implantation: a potential tool to reduce insertion trauma and improve preservation of residual hearing

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Abstract

Hearing and cochlear microstructure preservation remains challenging and a goal to achieve during and after cochlear implantation. Improvement of the implant design, imaging-driven choice of the electrodes array, soft surgical approaches, robot-assisted insertion are factors that have improved the residual hearing preservation rate. However, more than 50% of the CI patients still lose their residual hearing postoperatively. Other tools are needed, like Electrocochleography (ECochG).
Intracochlear ECochG records the acoustically evoked potentials that are produced by outer and inner hear cells or by neural structures. Cochlear Microphonic (CM), Auditory Neurophonic (ANN), the composite action potentials (CAP) may be used to analyse and follow cochlear health during and after cochlear implantation. Continuous tracking of CM during insertion is particularly studied. It can allow a real-time feedback of Hair cells health during the implant placement. CM signal modifications are used to drive the insertion procedure: when the amplitude dropped during advancing the electrode array, the insertion is paused, or the array is pulled back slightly.

Multiple studies have shown correlation between hearing loss and intracochlear ECochG changes during surgery. CM modifications are frequently used to detect a risk of cochlear trauma and residual hearing loss. In general, three possibilities could be observed: CM amplitude increased until the end of the insertion, fluctuating drops or drops without recovering. The first seems to show the smallest loss of acoustic hearing. However, simple correlations between intraoperative measurement of CM amplitudes and hearing preservation cannot easily be made. Indeed, decreases of CM amplitude may be associated with preserved hearing if phase changes (or distorsion)s of the curves are also present. Therefore, the phase and the amplitude of the signal should both be considered. The prognostic is worse in case of CM decrease without phase shift.

Predictive value for hearing preservation of ECochG changes during cochlear implantation remains under discussion. More data are needed to better understand the impact of the different signals and the nature of the fluctuations during insertion.
Finally, robot-assisted electrode insertion, controlled by the intraoperative ECochG, provides an additional opportunity to continuously assess and modify the insertion speed and axis of the electrode array, as well as to improve ECochG understanding.

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The Challenges in Preserving Residual Hearing in Cochlear Implantation

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Abstract

Electric-acoustic stimulation (EAS) has emerged as a standard treatment for patients with high-frequency hearing loss. EAS is usually performed with shorter electrodes of 16–24mm in length. However, it should be noted that high-frequency hearing loss is more or less progressive; therefore, the natural course of hearing should be considered for patients with residual hearing. From this perspective, a complete solution is expected to require the use of longer electrodes to cover the entire cochlea (Yoshimura et al., 2020). Our series of studies indicated that residual hearing can be preserved even after the insertion of longer electrodes. To assess the benefit of EAS with long electrodes, we analyzed the results of hearing preservation (HP) and speech perception outcomes for EAS.

Patients with residual hearing (low frequency with a threshold < 80dBHL for the average of values at 125, 250 and 500 Hz before implantation) were enrolled for the present study. A MED-EL Flex 28 (28mm) electrode was implanted and, following evaluation of post-operative residual hearing, a SONNET EAS audio processor was fitted to provide acoustic stimulation where applicable.
Residual hearing was preserved in all patients. All patients received acoustic stimulation in the low frequencies, with improvement in speech perception observed. With regard to the factors affecting HP, age at implantation showed a slight correlation, while it was independent of pre-operative low-frequency hearing thresholds, cochlear duct length, and electrode length. We confirmed that HP is possible with longer electrodes, and the addition of acoustic stimulation appears to improve hearing ability. A recent systematic review supports the view that longer electrodes provide HP rates comparable to those observed for medium-length electrodes (van de Heyning et al., 2022). With regard to the benefits of EAS in terms of speech perception, speech perception in noisy conditions was improved by adding acoustic stimulation. From an etiological perspective, we have successfully identified variants in the *CDH23, SLC26A4,* and *LOXHD1* genes. In our series of EAS surgeries, HP rate was particularly good for patients with stereocilia-related gene mutations (such as *CDH23*). In conclusion, hearing loss associated with these genes has been reported to be progressive; therefore, future patient audiograms should be considered when choosing the appropriate intervention.

*Speaker

Dexamethasone Eluting Electrode and Drug A acts synergistically to preserve residual hearing in an animal model of cochlear implantation.

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Abstract

Background: Pharmaceutical interventions holds a great potential for the preservation of residual hearing post-cochlear implantation. Intracochlear drug delivery is promising, but there are challenges in reaching and protecting all regions of the cochlea.
Objective: To evaluate the combined efficacy of a novel otoprotective drug (drug A) deliv-ered through a cochlear catheter with a dexamethasone eluting electrode (Dexel) on residual hearing preservation in a preclinical rat model of cochlear implantation.

Methods: The animals were divided into 9 groups: 1) Control; 2) animals implanted with a cochlear implant (CI); 3) animals implanted with a Dexel (Dexel); 4) Canula elution of Ringer lactate (Can + Ringer); 5) Canula elution of Ringer lactate and implantation of animals (Can+ CI); 6) Canula elution of Ringer lactate solution and animals implanted with Dexel CI (Can + Dexel); 7) Canula elution of drug A at 5mM (Can A5); 8) Canula elution of drug A at 5mM and implantation of animals (Can A5+ CI); 9) Canula elution of drug A at 2mM and animals implanted with Dexel CI (Can A2+ Dexel). Hearing thresholds were determined in each group pre-operatively, day 7 and day 30 post-cochlear implantation, using auditory brainstem responses (ABRs). Organ of Corti dissections were performed for each group at day 30 post CI. Immunostaining was performed to determine hair cell (HC) damage and oxidative stress markers.

Results: Hearing threshold shifts at day 7 and 30 of groups treated with drug A (Can A5 or A2 + CI, Can A2+ Dexel) were lower than the CI or Dexel group. HC viability and Oxida-tive stress presence were not statistically different to controls for Can A2+ Dexel group.

Conclusions: Canula delivery of drug A at 2mM and cochlear implantation with the dexamethasone eluting electrode have a synergistic effect allowing preservation of residual hearing in all cochlear turns.

Grant support: (2) MEDEL GmbH

*Speaker

"Noise-induced and age-related hearing loss in humans and animals: new insights and novel therapies"

Charles Liberman*[1]

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Abstract

It was long believed that hair cells were the most vulnerable elements in the ear and that auditory-nerve fibers (ANFs) die only after the hair cells have died. We showed this was not true, i.e. that the most vulnerable elements, in both noise-induced and age-related hearing loss, and in both human and animal ears, are the synaptic connections between ANFs and inner hair cells (IHCs). This synaptopathy can silence large numbers of ANFs, but it does not affect audibility, or the audiogram, until it is nearly complete. On the other hand, this ANF disconnection significantly impairs intelligibility, and likely explains why problems hearing in a noisy environment are so widespread. This talk will review recent histopathological data from our lab, at both the light and electron microscopic levels, demonstrating the nature and extent of synaptopathy in both human and animal cochleas, as well as electrophysiological and behavioral data from human subjects gathered in search of reliable biomarkers of the ANF degeneration that hides behind a standard clinical audiogram.

*Speaker

Vestibular Implantation and Long-Term, Continuously Motion-Modulated Stimulation to Treat Patients Disabled by Bilateral Vestibular Hypofunction

Andrianna I Ayiotis[1,2], Margaret R. Chow[1,2,3], Desi Schoo[1,4], Celia Fernandez Brillet[1,2], Peter J. Boutros[1,2], Kelly Lane[1,4], Stephen P. Bowditch[4], Yoan Gimmon[4], Claudia Lee[1,2], Brian J Morris[1,2], John Carey[4], and Charles C. Della Santina[*1,2,4]

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Abstract

Background & Objectives: Adult-onset bilateral vestibular hypofunction (BVH) causes chronic disequilibrium, blurred vision during head movement, postural instability and difficulty walking. Since 2016, we have performed a clinical trial of continuous (24hr/day or all waking hours) motion-modulated prosthetic stimulation. A unilateral vestibular implant (VI) system developed by Labyrinth Devices LLC and MED-EL GmbH delivers frequency- and amplitude-modulated current pulses targeting the vestibular nerve's three semicircular canal branches.

Methods: Ten subjects (5 male, 5 female, 55-65 years old, symptom duration 3-24 years) with adult-onset BVH underwent unilateral implantation from 2016 to 2021. Seven had ototoxic loss; 3 had idiopathic loss. Five surgeries were outpatient; we observed 5 patients overnight. We assessed vestibulo-ocular reflex (VOR) responses to head rotation, pure tone and speech audiometry, dynamic visual acuity, clinical tests of posture and gait, and patient-reported outcome instruments quantifying disability and health-related quality of life.

Results: Every participant has used the VI continuously since activation. Six wear it 24 hr/day; 4 wear it except when in bed. All have prosthetically evoked VOR responses for each of three implanted canals, typically ranging from 5-50∘/s and approximately aligning with the target canal's axis. VOR responses during head rotation are greater with motion-modulated stimulation than without. Constant rate, constant amplitude prosthetic input – a placebo control – yields no apparent benefit, consistent with *a priori* expectations because it conveys no motion information. Posture, gait, dizziness handicap, dizziness, disability and

*Speaker

SF36-derived health-related quality of life improved from preop for the group. Six of ten implanted ears retained hearing sufficient for unaided communication.

Conclusions: Outpatient vestibular implantation can be performed safely. Improved postural stability, gait, patient-reported disability and quality of life suggest motion-modulated prosthetic vestibular stimulation is an effective treatment for BVH. Hearing preservation is possible and appears more likely when intralabyrinthine fluid spaces are isolated from the mastoid.

Support & Disclosures: NIDCD R01DC013536, U01DC019364; Labyrinth Devices, LLC; MED-EL GmbH; NIA R01AG076701. We thank Mehdi Rahman, Nicolas Valentin and the MED-EL Vestibular Implant Systems group. CCDS holds equity interest in Labyrinth Devices, LLC and royalty interest in patents assigned to Johns Hopkins University (JHU). The terms of this arrangement are managed in accordance with JHU policies on conflicts of interest.

The cochleo-vestibular implant: update and remaining challenges

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Abstract

Bilateral vestibulopathy is a chronic and disabling condition that significantly affects the quality of life of affected patients and for which there is currently no established treatment. However, electrical stimulation of the vestibular system has shown very promising results. "Pure" vestibular implants aim at restoring the function of the semicircular canals or otolithic organs, cochleo-vestibular implants allow to restore the auditory function at the same time, galvanic stimulators use the principle of stochastic resonance and allow to optimize the residual vestibular function. All the research teams working with these different prototypes, which use electrical stimulation of different modalities and target different anatomical structures, have demonstrated significant effects on certain aspects of vestibular function. However, there are still several steps to be taken before a commercial product can be considered. The Geneva-Maastricht team has been working since the beginning on the development of a cochleo-vestibular implant. To date, 22 patients with bilateral vestibulopathy of heterogeneous etiologies have been implanted with different cochleo-vestibular implant prototypes targeting the restitution of semicircular canal function and auditory function. Quantification of functional and clinical benefit, precision of electrode placement, cochleo-vestibular interactions and vice versa are among the challenges we are currently facing. With the recent completion of a wearable processor that simultaneously processes motion and auditory information, the collection of data in the patients' living environment has begun. This data will probably be decisive for the future development of our cochleo-vestibular implant concept.

*Speaker

Restoration of Vestibular Function by Regeneration of Type I and Type II Hair Cells in Mature Mouse Utricle

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Abstract

Background: The vestibular sensory organs of the inner ear contain highly specialized mechanoreceptive hair cells essential for balance. Vestibular hair cells regenerate spontaneously in response to damage; however the extent of regeneration declines after the first postnatal week. In this study, we sought to develop a pharmacological treatment to enhance vestibular hair cell regeneration in adult utricle.
Methods: We used adult mice that express the diphtheria toxin receptor in hair cells (Pou4f3-DTR) for targeted ablation of hair cells. Mice received a unilateral injection of small molecules, a combination of a glycogen synthase kinase inhibitor (CHIR99021) and histone deacetylase inhibitor (valproic acid), after systemic administration of diphtheria toxin. This combination of drugs, previously shown to stimulate supporting cell proliferation and hair cell differentiation in cochlear organoids, was delivered locally via the semi-circular canal, and the extent of spontaneous vs drug-induced regeneration was compared between the treated and untreated (contralateral) ear

Results: We observed a significant increase in cells expressing hair cell marker, MYO7A, in drug-treated ears relative to ears without treatment where hair cells regenerated spontaneously. Drug treatment resulted in regeneration of 58% of the normal number of hair cells after 8 weeks as compared to 32% in the DT-treated ear without drug treatment. Lineage tracing of supporting cells showed newly regenerated type I and type II vestibular hair cells identified by immunoreactivity to MYO7A and SOX2 antibodies, with MYO7A+SOX2- being type I hair cells while MYO7A+SOX2+ co-labeled cells specific to type II hair cells. Changes in hair cell number were associated with a significant functional improvement as assessed by the vestibuloocular reflex and single fiber recordings from vestibular neurons.
Conclusion: This work provides further knowledge of the molecular mechanisms required for vestibular hair cell differentiation and suggests that the drug combination may be a candidate for clinical application for balance disorders related to loss of hair cells.

Keywords: Vestibular hair cells, regeneration, drug treatment

*Speaker

Assessing the Potential of Adeno-Associated Virus Serotypes to Target the Hair Cells of the Human Inner Ear for Gene Therapy

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Abstract

Background : The effectiveness of viral gene therapy for inner ear diseases depends on many factors, including viral cell tropism, and animal species. While Recombinant Associated-Adenovirus (AAV) the most commonly used vectors, and their tropism is well characterized in preclinical models, little is currently known about their efficacy in human inner ear application.
Objectives : The aim of this study is to examine the cellular tropism of commonly used AAV serotypes in preclinical animal models through human inner ear explants.

Methods : Membranous labyrinth of semi-circular canals and utricule were collected during translabyrinthine surgeries, primarily for resection of vestibular schwannoma. Following dissection, the ampullar cristae and utricular maculae were cultered, and transduction was carried out using an AAV vector containing the Green Fluorescent Protein (GFP) gene under the control of CMV promoter. The transduction rate was assessed using GFP immune labelling and confocal imaging.

Results : We first developed a technique for sampling and culturing and confirmed the presence of vestibular hair cells after 3 days of culture. Then, we evaluated the tropism of 7 AAV serotypes, and all but two serotypes showed a satisfying transduction rate for vestibular hair cells, up to 52% of cells. However, the use of a non-specific promoter results in the transduction of other cell types such as fibroblast or neurons.

Conclusions : This study identifies successfully identified AAVs capable of transducing sensory cells in the inner ear. These results are promising for the future application of viral gene therapy in inner ear diseases in Human.

Aknowledgement :
We would like to aknowledge the Centre de Recherche Translationnelle of Institut Pasteur (Paris) for their help in setting up the study.

*Speaker

AAV gene therapy and iPS cell-based drug development targeting cochlear gap junction

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Abstract

Mutation of the Gap Junction Beta 2 gene (*GJB2*) is the most frequent cause of hereditary deafness worldwide and accounts for up to 50% of non-syndromic sensorineural hearing loss. *GJB2* encodes connexin (CX) 26, a component of the cochlear gap junction. We demonstrated that the degradation of the gap junction plaque (GJP) macromolecular complex composed of CX26 and CX30 is a critical feature of the pathogenesis and begins during the embryonic stage (Kamiya, J Clin Invest, 2014). We also showed that the cochlear gene delivery of *GJB2* using Adeno Associated Virus (AAV) significantly restored the GJPs and improved the auditory responses of CX26-deficient mice (Iizuka, Hum Mol Genet, 2015). To optimize for inner ear gene delivery, we shuffled and modified wild-type AAV capsid sequences and selected for efficient AAV vectors. For disease modeling to assess the AAV vectors, we developed a novel strategy to differentiate induced pluripotent stem (iPS) cells into functional CX26-GJP-forming cells that exhibit physiological properties typical of the developing cochlea (Fukunaga, Stem Cell Reports, 2016). And finally, we generated human iPS cells from patients with common Japanese and other East Asian *GJB2* mutations, GJB2 p.V37I, G45E/Y136X, and 235delC, and generated their disease model cells with the gap junctions (Fukunaga, Hum Mol Genet, 2021). The disease model cells derived from these patient iPS cells were used to develop biopharmaceuticals and new AAV vectors for GJB2 related hearing loss.

Keywords: GJB2, Gap Junction, AAV, iPS cell, Gene therapy

*Speaker

SENSORINEURAL DEAFNESS: FROM GENETIC ARCHITECTURE TO GENE THERAPY

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Abstract

Progress in deciphering the genetic architecture of human sensorineural hearing impairment (SNHI) and multidisciplinary studies of mouse models have led to the elucidation of numerous molecular mechanisms underlying auditory system function, primarily in the cochlea (the mammalian hearing organ). The studies have also provided unparalleled insight into the pathophysiological processes involved, paving the way for the development of inner ear gene therapy. The 10 years of gene therapy approaches in these models, based on gene replacement/augmentation and gene editing, and also on antisense oligonucleotides (ASOs), small interfering RNA (siRNA)-related or RNA-editing approaches to prevent and/or cure monogenic SNHI forms and associated balance disorders, highlight current translation opportunities. The talk will discuss the advances in inner ear gene therapy development, the key specific challenges faced and the unresolved issues that must be addressed for inner ear gene therapy to meet high quality standards worldwide, ensuring effective and safe procedures.

The work in the author's laboratory has been supported by European Research Council, Fondation pour l'Audition (FPA IDA05), Ile de France (DIM Thérapie génique), PRESAGE (ANR-21-CE14-0075), RHU AUDINNOVE (ANR-18-RHUS-0007) and SENSORION.

*Speaker

Progress and Challenges in the Development of In Vivo Gene Therapies with AAV Vectors

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Abstract

In vivo gene therapy offers several potential advantages over conventional therapeutic modalities. These include the long-term duration of effect after a single intervention, the ability to target genetic defects and pathways by directly expressing a transgene of interest, and the possibility of delivering a therapeutic gene directly in the tissue/cell where it is needed. Thus far, the most broadly adopted platform for in vivo gene therapy is based on adeno-associated virus (AAV) vectors, which are viral vector derived by viruses isolated in nature or engineered to achieve a desired tissue tropism. Several preclinical and clinical trials have shown that AAV vectors have a favorable safety and efficacy profile, and regulatory approval was obtained for gene therapies for congenital blindness, spinal muscular atrophy, hemophilia, and other genetic diseases. Emerging long-term follow up data are also encouraging, showing multi-year efficacy in most cases. In recent years, the steep increase in gene therapy trials has highlighted key challenges to the platform. Immunogenicity appears to limit efficacy and has been linked to toxicities in humans, particularly when high doses to AAV vector were administered systemically. Delivery to closed compartments like the CNS, the eye and the brain has also been an area of steady innovation, to improve delivery methodologies, achieve better targeting of cells of interest, and limit potential local toxicities. To this aim, the development of delivery devices, AAV vectors with improved tropism, and enhanced design of expression cassettes, along with enhanced vector manufacturing technologies, has been instrumental to the overall advancement of the platform. Immunomodulatory regimens are also in development, to address inflammatory responses associated with gene transfer, and to allow for vector dosing and re-dosing in the presence of anti-capsid antibodies. Novel delivery technologies, currently in development, may further enhance the future potential of in vivo gene therapy.

*Speaker

Disease-modifying therapy for autosomal dominant hereditary hearing loss in DFNA9

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Abstract

DFNA9 is the most frequent hereditary disorder in Belgium and the Netherlands causing hearing loss at 20-30 years and evolving towards deafness by 60-70 years. Additionally, patients suffer from bilateral vestibulopathy by the age of 40 years. Over 30 different pathogenic variants in the COCH gene have been reported worldwide. Currently, there is no cure available although we can restore speech understanding to some level with hearing aids and cochlear implants. Ideally, a disease-modifying therapy would have the ability to delay or stop the progression of hearing loss in DFNA9. In DFNA9, only one of the two copies of the *COCH* gene (one inherited from either parent), is mutated and encodes for a toxic protein that affects the aging inner ear in general, and the spiral ligament and spiral limbus more specifically. It therefore presents us with a target anatomically as well as genomically. The DFNA9 population is particularly relevant to develop and evaluate a disease-modifying gene therapy for sensorineural hearing loss because: potential carriers are aware of their hearing-impaired relatives, potential carriers can get routine genetic testing and know their carrier status, once aware of their carrier status, a significant pre-symptomatic stage of several years starts, carriers are aware they will inevitably develop severe-to-profound SNHL and are open to future clinical trials with gene therapy, as identified during a patient advocacy meeting.

*Speaker

Gene editing rescues hearing in the Shaker-1 mouse model of Usher syndrome type-1B

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Abstract

Background: Usher 1B Syndrome is an autosomal recessive inherited disorder that presents with progressive sensorineural hearing loss, vestibular dysfunction, and tunnel vision within the first decade of life. The majority of cases are caused by mutations in *MYO7A*, a gene which encodes for an actin-binding motor protein found in inner and outer hair cells (HC) important for the movement of intracellular proteins along the actin filaments of HC stereocilia. *Shaker-1* is a mouse model for Usher 1B with a *MYO7A* mutation causing hearing loss, circling behavior, and head tossing phenotype. While Myosin VIIA is only expressed in inner and outer HCs, *Shaker-1* -/- mice have unexpected diffuse cochlear damage including loss of spiral ganglion neurons and thinning of the stria vascularis and *Shaker* 1 +/- mice develop a progressive hearing loss starting 5 months of age. The underlying mechanism of this diffuse cochlear damage is unknown.
Methods: Guide RNA targeting the Shaker 1 mutation and Cas9 were loaded into mesenchymal stem cell derived extracellular vesicles. Crispr-Cas9 EVs were injected into the posterior semicircular canal of P3 Shaker mice. Heterozygous treated and untreated, and homozygous mutant *Shaker-1* mice underwent hearing testing at varying ages (2 weeks, 1 month, 3 months, 6 months, and 1 year). Cochleae were then harvested and immunohistochemistry (IHC) for .: Annexin-5 (Ann-5) 1:200, 4-Hydroxynonenal (4-HNE) 1:50, and 3-Nitrotyrosine (3-NT) carried out.

Results: Markers for apoptosis (Ann-5) and oxidative stress (4-HNE, 3-NT) were present in HT and HM mice but absent in WT mice. Ann-5 was most strongly expressed in inner and outer HCs at all ages. Notably, 4-HNE and 3-NT expression was found in inner and outer HCs, supporting cells, and the spiral ligament as early as 2 weeks in both HT and HM mice with continued expression at 1 month and 3 months of age. By 6 months, 4-HNE and 3-NT was strongly expressed throughout the spiral ligament (1 year data). Mice treated

*Speaker

with EVs demonstrated effective gene editing and preservation of hearing with lower degrees of oxidative stress compared to undtreated HT mice.
Conclusions: Shaker-1 HT and HM mice show increased expression of Ann-5, 4-HNE, and 3-NT diffusely throughout the cochlea as compared to WT mice, suggesting that oxidate stress may play a role in diffuse cochlear damage. EVs can act as an effective delivery vector for gene editing components resulting in rescue of hearing in Shaker 1 +/- mice.

From Big Data to Gene Therapy - Precision Medicine for Deafness

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Abstract

Precision medicine, a rapidly developing field that uses data-driven approaches, offers new hope for people with deafness. This approach provides the opportunity for early diagnosis and precise treatments for individual patients based on their own unique genetic profile. Precision medicine has become increasingly crucial for hearing loss as it affects millions of people worldwide and has been shown to have major consequences at the social and psychological levels in children and adults. Therefore, determining the genetic background is fundamental for early clinical management, risk assessment, and developing personalized treatments. To date, over 150 genes have been identified to be associated with deafness, however, it is estimated that about half of the inherited deafness cases in the Israeli Jewish and Palestinian Arab populations remain unsolved. To address this issue, a large-scale study is being conducted on the hearing-impaired population in Israel using the KSM TipaBiobank. Next-generation sequencing (NGS) is being performed on 1200 adult deaf individuals from the Biobank, and pathogenic variants are being evaluated to determine genotype-phenotype-ethnicity correlations. Personalized genetic counseling is provided based on the identified variant, and novel variants are being functionally characterized in the lab using knock-in mouse models by in-vitro cell culture assays and CRISPR/Cas9 technology. Next, gene therapy experiments are performed, using different tools to rescue both auditory and vestibular functions in mouse models for deafness, with the perspective of treating human deafness in the future. The combination of gene therapy and precision medicine has great potential to revolutionize healthcare and provide personalized treatments for individuals with genetic hearing loss. Research funded by the Israel Precision Medicine Partnership Program 3499/19

Keywords: Big data, genetics hearing loss, gene therapy, high, throughput sequencing

*Speaker

Implantation of neural progenitor cells derived from human induced pluripotent stem cells improves sensorineural hearing loss in mouse model

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Abstract

Sensorineural hearing loss is a common disease caused by aging, ototoxic drugs or exposure to noise. Since sensory hair cells and neurons in the inner ears are unable to spontaneously regenerate, damage to these cells would cause permanent hearing loss. Patients suffering from hearing impairment may have difficulty communicating with people or have lower quality of life. Currently, there is no curative treatment for sensorineural deafness. Induced pluripotent stem cells (iPSCs) that have the potential to differentiate into all cell types provide a great opportunity for cell-based regenerative therapy in a variety of diseases including neurological dysfunction. Herein, we conducted a proof-of-concept study to test the hypothesis that implantation of iPSC-derived neural progenitor cells (iPSC-NPCs) is capable to repair hearing loss in the mouse model of ouabain-Induced cochlear nerve degeneration. We established a differentiation platform for generating high quality iPSC-NPCs expressing more than 95% of NPC-related protein markers (Sox2, Nestin, and Pax6). While mice treated with ouabain exhibited significant elevations of auditory brainstem responses (ABR) thresholds and loss of spiral ganglion neurons (SGNs) in the cochlea compared to the untreated control animals, a decrease in ABR threshold at each frequency (12, 24 and 32 kHz) with increased SGNs intensity were observed in the affected mice receiving one dose of iPSC-NPCs though round window niche injection. Our data provide the first demonstration that iPSC-NPCs may be used as a therapeutic modality for patients with severe sensorineural hearing loss with the advantage of both function improvement and tissue architecture restoration. Further characterization of the mechanism of action of iPSC-NPCs on the modulation of SGNs regeneration is warranted to translate these findings to the clinical setting.

Keywords: induced pluripotent stem cells, neural progenitor cells, ouabain, spiral ganglion neurons

*Speaker

Design, Manufacture and First Clinical Application of an Additively Manufactured Patient-Individualized Drug Releasing Round Window Niche Implant to Treat Idiopathic Sudden Sensorineural Hearing Loss

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Abstract

Introduction: We developed a drug releasing, patient-individualized round window niche (RWN) implant (RNI) for local inner ear pharmacotherapy.
Methods: The workflow for the production of the RNI starts with computed tomography data of the target region. A software for semi-automatic segmentation of the RWN adds a handle to the segmented RWN volume comprising the individual implant shape. The RNI is 3D-printed using dexamethasone containing silicone. In vitro and in vivo tests were performed before the RNI was used in five named patients suffering from idiopathic sudden sensorineural hearing loss (ISSHL), where the first line therapy did not show improvement.

Results: The software helps the user to create a better defined segmentation compared to manual slice by slice segmentation in shorter time. The dexamethasone containing silicone is 3D-printable in individualized RNI volumes and shapes. The printed specimens were sterilizable, biocompatible and induced anti-inflammatory effects in vitro. In animal trials no implantation related otogenic complications such as vertigo or fibrotic RNI encapsulation were observed. Individualized RNIs were printed for specific human cadaver temporal bones and fitted well into the respective RWN. In the first individually implanted patients the hearing thresholds of 2 patients were stable 29 days after RNI insertion, and an improvement of more than 10 dB in $\geq$ 3 frequencies was observed in 3 patients.

Conclusion: The patient-individualized drug releasing RNI was safely inserted into the RWN, no adverse events were observed and it seems to effectively treat ISSHL in individual treatment of named patients. Subsequent clinical trials are needed to prove the safety and efficacy. Next to ISSHL therapy, applications in Cochlea Implant (CI) settings to treat CI related pathologies such as fibrosis and residual hearing loss, and other pathologies which may benefit from local drug delivery off patient-individualized implants such as chronic sinusitis will be addressed in future studies.

Keywords: individualized therapy, patient specific implant, local drug delivery, intratympanic, pharmacotherapy, dexamethasone, hearing loss

*Speaker

Hidden hearing loss: pathogenic mechanisms and potential therapeutic approaches

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Abstract

Hidden hearing loss (HHL), a recently described auditory disorder, has been proposed to affect auditory neural processing and hearing acuity in subjects with normal audiometric thresholds, particularly in noisy environments. In contrast to central auditory processing disorders, HHL is caused by defects in the cochlea, the peripheral auditory organ. Noise exposure, aging, ototoxic drugs and peripheral neuropathies are some of the known risk factors for HHL. Our knowledge of the causes and mechanisms of HHL are based primarily on animal models. However, recent clinical studies have also shed light on the etiology and prevalence of this cochlear disorder and how it may affect auditory perception in humans. In my talk I we review the current knowledge regarding the causes and cellular mechanisms of HHL, summarize information on available noninvasive tests for differential diagnosis, and discuss potential therapeutic approaches for treatment of HHL.

*Speaker

Challenges in Severe Deafness Rehabilitation by Conventional Hearing Aids

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Abstract

BIAP classification defined severe deafness as a lack of audibility comprised between 70 and 89 dB HL (average of tonal audiometric thresholds at 4 frequencies). Conventional hearing aids are sophisticated hearing devices allowing gain control from 0 to 70 dB but the outcomes with hearing aids depends on the aetiology of deafness: an otosclerosis with a pure Rinne will benefit of a strong gain with a good intelligibility score although a Meniere disease with the same degree of hearing loss will not.
Nevertheless, pre-fitting rules to calculate hearing aids gain are based on these tonal audiometric thresholds measured with headphones or directly through the hearing aids.

Although 'severe deafness' is a symptom and not a disease, 80% of adult patients have unknown aetiology, and the diagnosis often refers to the degree of hearing loss. Conversely, 80 % of deafness at birth are well known genetic forms. This knowledge helps the professionals over the right conduct to adopt.

In France, hearing aids prescription in adults required tonal audiometric test and speech intelligibility tests in quiet and in noise. Much more functional and medical informations are suitable to fit hearing aids and to know what to do. In the absence of these data, hearing aid fittings are a supplementary functional exploration of the auditory system by trying different fitting solutions. Then, the first daily challenge for the audiologist becomes to determine an empirical fitting, and to find a balance between comfort and effectiveness for each patient by different trials.

Also, the 2d challenge could be to determine in adults the phenotype of genetic deafness by an appropriate protocol of functional tests. It will open the field to an oriented hearing aid fitting by adequate objective and subjective measures.

The 3d challenge is to be able to drive retrospective analysis, managing big data including medical, genetic, imaging, questionaries, results of subjective and objective functional tests, hearing aid fittings and evaluations.

The 4th challenge is to bring strong objective arguments which could enlarge cochlear implant indications in adults with severe hearing loss.
To take up these fascinating challenges will allow us to have a better knowledge of severe deafness and the conditions of its rehabilitation by hearing devices.

*Speaker

Hearing care for severe to profound hearing losses. Hearing aids, cochlear implants, bimodal hearing : a short review.

Lionel Vanderkerken*[1]

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Abstract

A review on the state of the art, our guidelines and daily practice at the audiophonology center in Brussels Stluc, regarding severe to profound hearing impairment treatment and care.

Keywords: Hearing loss, Hearing aid, Cochlear implant, Bimodal stimulation, Electracoustic stimulation

*Speaker

PROGNOSTIC FACTORS OF HEARING AIDS OUTCOMES:A big data analysis

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Abstract

Background
The goal of the presentation is to analyze a large database of 169144 patients to:
To measure the influence of socioeconomic factors on access to hearing Aid
To evaluate the impact of technology on outcomes

Methods
The data included patients profiles, clinical history, audiological evaluations, brand signal processing, fitting The prediction of understanding used an algorithm XGBoost and the interpretability
the Shap Value

Results
Based on ecological deprivation index there was 15 years difference in access to hearing aid between low and high socioeconomic levels
The mean improvement PTA 21dB, Speech in Quiet 11dB , Speech in noise 2.8dB
The determinant factors was Age ,Technology, Quality of fitting

Conclusion
Global results must be interpreted cautiously there is a need for supervised IA and clustering

*Speaker

Could the Genetic Origin of Sensorineural Hearing Loss Affect the Outcome of Cochlear Implantation?

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Abstract

Among the various etiologies observed in cochlear implant (CI) or electric acoustic stimulation (EAS) patients, genetic etiologies are believed to be the major cause of hearing loss. Genetic diagnosis ensures a more accurate diagnosis and suitable clinical interventions based on the predicted phenotype. More than 100 responsible genes have been reported to be associated with non-syndromic hearing loss and we have recently clarified the genetic etiology of 10,047 hearing loss patients (Usami and Nishio, 2022). When focusing on patients receiving CI/EAS, those possessing certain types of deafness gene mutation have achieved satisfactory auditory performance, suggesting that the identification of the genetic background facilitates the prediction of post-CI/EAS performance (Usami et al., 2020).

To clarify genetic etiology of deafness, a common platform using a diagnostic DNA panel carrying 63 deafness genes together with a common filtering algorithm were applied to 10,047 samples obtained from patients undergoing social health insurance-based genetic testing for hearing loss in Japan. In addition, patients receiving CI/EAS were analyzed from a genetic perspective.

The most remarkable result obtained in our comprehensive study was that the data allowed clarification of the genetic epidemiology from congenital/early-onset deafness to late-onset hearing loss. The overall diagnostic rate was 38.8%, although the rate differed for each age group; 48.6% for the congenital/early-onset group (_˜5 y.o.), 33.5% for the juvenile/young adult-onset group, and 18.0% for the 40+ y.o. group. It was also revealed that the types of genes differed within the groups according to severity; i.e., *GJB2*, *SLC26A4*, and *CDH23* were more commonly found in the severe-to-profound hearing loss group (which is an indication for CI/EAS). Interestingly, each age- and severity-based subgroup showed a different type of causative gene. Our comprehensive review clarified the detailed clinical characteristics (onset age, severity, progressiveness, etc.) of hearing loss caused by each gene, and will provide useful information for future clinical applications, including genetic counseling and selection of appropriate interventions. Genetic screening successfully identified the causative mutation in CI/EAS patients. As expected, patients with specific deafness gene mutations showed relatively good results. Further, patients possessing mutations in a number of deafness genes known to be expressed within the inner ear achieved satisfactory auditory performance, suggesting that the identification of the genetic background facilitates the prediction of post-CI performance. Therefore, determination of the involved region inside/outside of the cochlea by identification of the responsible gene is essential.

*Speaker

Cochlear implantation in inner ear malformations

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Abstract

Congenital hearing loss can be due to membranous abnormalities of the cochlea , representing the majority of cases (80%), and which are not detected by current imaging (MRI , CT) or to bone abnormalities (20 %), which contitute a real surgical challenge, due to surgical difficulties and management problems. During implantation,there may be abnormalities in the path of facial nerve , geyser, difficulty identifying the cochlea and round window, and misplacement of the elecrode array. The surgeon must be able at all times to modify the surgical approch, and choose the appropriate electrode array according to the type of malformation. The audiologic findings depend mainly on the status of the cochlear nerve.

*Speaker

Management of difficult cases in cochlear implantation: from anticipation to achievement

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Abstract

Background
Cochlear implantation is a well-codified surgical procedure which is possible to achieve in almost all cases. But in some patients, real surgical challenges can impede cochlear implantation

Objectives: By analyzing several difficult cases when cochlear implantation was hard ot perform, we can give some advises to anticipate difficulties, and to facilitate the surgical cochlear implantation.
Conclusion: Precise and exhaustive preoperative imaging is mandatory. CT-scan of the labyrinthine capsule can detect anatomical variations, not only of the cochlea but also of the facial nerve. It can show contracted mastoid, closeness of sigmoid sinus or low linea temporalis. Preopaerative MRI can alert for cochlear fibrosis and lack of cochlear nerve. Combined transmeatal transmastoid approach can give optimal control of EA-insertion. Fluoroscopy can help to achieve a cochlear insertion in some difficult anatomical cases, e.g., far advanced otosclerosis or malformed cochlea.

*Speaker

Cochlear implantation in inner ear malformation

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Abstract

Key words: Inner ear – Malformation – cochlear implant - surgery

Objective: The aim of our work is to report and describe the experience of cochlear implantation in patients with cochlear malformations while reporting the radiological aspects of these malformations, the difficulties, the possible surgical complications as well as the auditory and speech production results obtained.

Material and methods: This is a retrospective study of 10 cases with severe to profound sensorineural hearing loss and inner ear malformations, in the ENT department of Specialties Hospital in Rabat, during the period from December 2014 to April 2023. For each case we collected epidemiological, clinical, radiological, therapeutic and post-surgical data.

Results: Our patients were divided into 6 males and 4 females. All of them had cochlear malformations according to Sennaroglu 2002 classification.

Medel and Cochlear implants specific to cochlear malformations were used.

The follow-up period varied from 6 months to 3.5 years with an average of 21 months. Good attendance at speech therapy sessions was observed in 8 out of 10 patients. 71% of patients had good auditory perception after 6 months. The good results were correlated with a high parental investment and good attendance at speech therapy sessions.
Conclusion: CI can be successfully performed in cochlear malformations. There is a difference in hearing performance and speech production scores between patients with different types of malformations and patients without cochlear anomalies. It is important to assess the severity of the inner ear deformity in order to identify surgical difficulties and therefore manage each patient.

Keywords: Cochlear implants, Cochlear malformation, Sennaroglu

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Function, Dysfunction and Restoration of Sensory Transduction Channels in Auditory Hair Cells

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Abstract

Transmembrane Channel One (TMC1) is the central pore-forming subunit of sensory transduction channels in auditory hair cells of mice and humans. Structure-function studies from my lab and others have identified key TMC1 residues within transmembrane domains 4-7 that line the ion channel pore. Interestingly, a number of these residues are also targets of genetic mutations in humans that cause either dominant (DFNA36) or recessive (DFNB7/11) forms of hearing loss. To date, over a hundred mutations have been identified in human TMC1 that cause genetic hearing loss. To develop therapeutic approaches to treat TMC1 hearing loss patients, we have investigated several gene therapy strategies, including gene replacement for recessive loss-of-function mutations, gene disruption using CRISPR/Cas9 genome editing to selectively target dominant mutations and base-editing to repair native DNA point mutations. We have used mouse models with TMC1 mutations to develop TMC1 gene therapy and have achieved broad-spectrum recovery of auditory function, in some cases achieving hearing thresholds equivalent to those of normal hearing mice. We find the recovery is durable out to one year, the latest time point tested and in the case of base-editing the recovery is predicted to last a lifetime. This work is ongoing and plans are being made to advance TMC1 gene therapy to the clinic for treatment of hearing loss patients who carry TMC1 mutations. For this presentation I will review these therapeutic strategies and provide an update on the latest advances in our understanding of the basic biology of TMC1 structure and function as well as our translational efforts to develop TMC1 gene therapy.

*Speaker

Treatment of Autosomal Dominant Hearing Loss By In Vivo Delivery of Genome Editing Agents

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Abstract

Genetic hearing loss is estimated to affect one in 500 newborns. Increasingly genetic mutations have been associated with hearing loss in adult including aging populations. The AAV-mediated gene supplement approach has shown major progress to treat mouse models of human genetic hearing loss. The emergence of genome editing technology, due to its ability to make precise and permanent DNA changes, is becoming a new platform of treatment for human genetic diseases including hearing loss.
To apply genome editing to treat genetic hearing loss, many factors have to be considered. The onset of hearing loss is likely of paramount importance due to the completion of human inner ear development in the uterus, thus the cell types amenable to treatment after birth may be limited due to degeneration. Mutations in genes expressed in all major inner ear cell types have been found to underly genetic hearing loss, which requires the delivery of editing complex into diverse cell subtypes for effective treatment. Genetic transmission modes will require different strategies for treatment, including precision editing for recessive and allelic specific disruption for dominant mutations. Approaches beyond bespoke single gene mutations have to be developed.

We are developing different strategies to use versatile genome editing to treat mouse models of dominant human genetic hearing loss. By liposome mediated delivery of editing RNP (ribonucleoproteins), we demonstrated hearing rescue in mouse models of human dominant hearing loss DFNA36 and DFNA37, by NHEJ-mediated disruption of the mutations in *Tmc1* in the inner hair cells and *Atp2b2* in the outer hair cells, respectively. RNP delivery shows allelic specific editing with reduced off-target. We provide evidence that two mutations can be edited simultaneously to rescue hearing in a digenic mouse model of genetic hearing loss. To expand editing therapy in the fully mature inner ear that is required for clinical applications, we used AAV-mediated delivery of editing complex into the adult cochlea to target a mutation in microRNA *Mir96* that causes human deafness DFNA50. We demonstrate robust and sustained hearing rescue without off-target effect. Importantly we detected transient AAV-mediated Cas9 expression in the cochlea without integration of AAV at the editing site, supporting a safety profile by inner ear AAV delivery of editing complex. Editing therapy can benefit from novel transient delivery. We screened lipid nanoparticles (LNP) to identify highly efficient LNPs to deliver editing complex mRNA in multiple inner ear cells, which will expand the reach of editing to target more inner ear cells as potential treatments. Our work illustrates the potential of developing genome editing therapies for diverse forms of genetic hearing loss. Continuous explorations of the technology will likely lead to editing therapy for human genetic hearing loss in the future.

*Speaker

RNA therapies for Otogenetic disorders: current status

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Abstract

Hearing loss is the most common sensory deficit worldwide, affecting millions of individuals. Hearing impaired people are severely handicapped in our modern society that heavily relies on fast communication. Half of the cases with congenital hearing loss have a genetic origin. Although hearing aids and cochlear implants have significantly improved over time, they still cannot compete with natural hearing.
Several types of genetic therapies are currently being evaluated, each having their own advantages and drawbacks. Our main focus is the development of RNA therapies, using antisense oligonucleotides (ASOs). ASOs are small single-stranded oligo's that are complementary to (pre-)mRNA that can have different chemistries and modifications. Their chemical composition determines stability, mode of action, specificity and affinity for their target sequence. ASOs can be used in different flavors to modulate pre-mRNA splicing or to induce the allele-specific degradation of transcripts.
We have developed a pipeline consisting of different models and bio-informatic tools to predict and functionally assess suitable splice modulation targets based on a patient's genotype for both USH2A and USH2C. Furthermore, we have developed allele-specific gapmer ASOs to degrade mutant transcripts associated with late-onset dominantly inherited forms of hearing loss DFNA9 and DFNA21, for which mutations act via a non-haploinsufficiency disease mechanism.

*Speaker

Applications of dual-AAV gene delivery to mouse models of hereditary hearing loss

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Abstract

Hearing loss is a common disorder affecting nearly 20% of the world's population. Recently, studies have shown that inner ear gene therapy can improve the auditory function in several mouse models of human hereditary hearing loss. In most of these studies, the underlying mutations affect only a small number of cell types of the inner ear, for example sensory hair cells. Here, we applied inner ear gene replacement therapy to the *Ildr1:Ildr1Gt(D178D03)Wrst* mouse (*Ildr1w-/-*), a model of human DFNB42, a non-syndromic autosomal recessive hereditary hearing loss associated with *ILDR1* variants. ILDR1 is an integral protein of the tricellular tight junction complex and is expressed by diverse inner ear cell types, both in the organ of Corti and the cochlear lateral wall. We applied simultaneously two synthetic adeno-associated viruses (AAVs) with different tropisms to deliver *Ildr1* cDNA to the *Ildr1w-/-* mouse inner ear; one targeting the organ of Corti (AAV2.7m8), and the other virus targeting the lateral wall (AAV8BP2). We showed that combined AAV2.7m8/AAV8BP2 gene therapy (combined AAV-*Ildr1* gene therapy) improves the cochlear structural integrity and the auditory function in the *Ildr1w-/-* mice.

*Speaker

Gene augmentation therapy rescues hearing in a DFNB9 clinical mouse model of a thermosensitive auditory synaptopathy

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Abstract

Sound encoding relies on extremely fast and sustained synaptic transmission between cochlear inner hair cells (IHC) and afferent dendrites of the primary auditory neurons. This process requires otoferlin, a six C2 domain Ca2+ -binding transmembrane protein, that acts as a calcium sensor in IHC for exocytosis. Indeed, otoferlin triggers the final steps of synaptic exocytosis by ensuring rapid vesicular neurotransmitter release at IHC ribbon synapses. In humans, severe to profound deafness (DFNB9) has been linked to various mutations in the OTOF gene. Among these mutations is a deletion of glutamic acid at position 1804 in the C2F domain of otoferlin, which causes temperature-sensitive (TS) auditory synaptopathy in the affected patients. We have generated a Knock-in mouse model *Otof TS/TS* expressing the aforementioned deletion, which resulted in profound deafness. Immunolabeling and confocal imaging revealed that otoferlin expression is low, with an abnormal subcellular distribution. Of particular note is the absence of otoferlin in the basolateral zone of IHC where ribbon synapses are located. Exocytosis of *Otof TS/TS* IHC, as monitored by membrane capacitance measurements was nearly abolished, implying that abnormal otoferlin expression and subcellular distribution is the root cause of the observed profound deafness. We then ask whether gene augmentation therapy can override the mutated otoferlin and restore normal protein expression and hearing, similar to what we have previously reported for total otoferlin knockouts.
In order to achieve this goal, dual Adeno-associated virus (AAV)-mediated gene augmentation therapy was administered to *Otof TS/TS* mice at P2. The effectiveness of the gene therapy was assessed at later stages of development. Immunostaining and confocal microscope imaging analyzes revealed that gene augmentation therapy can effectively restore the expression and appropriate distribution of otoferlin in the IHCs of the mice that underwent treatment. As a result, IHC Ca2+-dependent exocytosis were rescued to wild level in *Otof TS/TS* mice leading to normal hearing. Interestingly using a GO and no GO task behavioral test, we were able to show that these treated mice were able to discriminate sound frequencies indicating near normal central auditory processing and hearing performance.

Keywords: Deafness, Gene therapy, Otoferlin, central auditory processing

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Robot-Based Cochlear Implant Insertion

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Abstract

To overcome limitation on the blood perilymph barrier for inner ear therapy, it has been proposed to perform local drug delivery, even direct intracochlear delivery. The limitation of such an approach is intracochlear trauma. Regarding this issue, enhancement of inner ear structure preservation during cochlear implantation can be a good model.
The insertion of the cochlear implant is a short step in the care of the implanted patient. In this context, any improvement in the technique of implant insertion and placement is of benefit to the patient. The current goal of cochlear implant surgery is maintaining the integrity of inner ear structures in every case and not only for hearing preservation.
RobOtol® (Collin, Bagneux, France) is a robotic arm device, designed to assist middle ear surgery and cochlear implantation and tele-operated by the surgeon. Different array devices from five manufactures (Advanced Bionics, Cochlear, Medel, Nurotron, Oticon) can be adapted to the robotic arm. RobOtol® allows a slow and constant insertion speed (0.1-0.3 mm/s) of the electrode array into the cochlea. It also offers the possibility to modify the insertion axis following the optimal axis of insertion within the basal turn of the scala tympani. Current surgical technique and postoperative imaging results will be detailed in this presentation. We will also give an insight on how coupling robotics and navigation may further reduce array trauma insertion

Keywords: Robotics, cochlear implant

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Robotic Assisted Cochlear Implantation: the Belgian Clinical Experience with the Hearo procedure

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Abstract

Background: The aim of Robot Assisted Cochlear Implantation (RACI) is to improve accuracy; reliability and repeatability of successful cochlear implant surgery to ultimately improve outcomes of cochlear impantation (CI). One of the limiting factors why navigation systems let along robots could not be popularized was the lack of their accuracy. In the last 5 years technologies are meeting with the precision and accuracy desirable for otologist. Recently, a Swiss system called HEARO has taken that hurdle and has proven to safely warrant middle ear access (Mario Caversaccio, Bern, Switzerland) and also inner ear access (Vedat Topsakal, Antwerp, Belgium). Here we elaborate on our clinical cases implanted with the HEARO system.
Aim:

The first aim is to describe the actual HEARO procedure. Secondly we report on the accuracy measurements in temporal bones. Finally we discuss the experience and results in the first 25 patients.

Methods and Materials:

The Hearo system consists of a robotic arm executing the drilling, a reference system to link the scan of the ear to the patient using the registration procedure and a dedicated facial nerve monitoring system to allow a save passage of the facial nerve. The associated equipment is a high precision (0.1mm) intra-operative mobile conebeam CT scan (CBCT: XCAT XL; Xoran Ltd., USA) and dedicated software to analyze the scan and to define the drilling pathway (Otoplan®, CAScination, Switzerland). The HEARO system aims for full cochlear coverage and soft surgery. Therefor it allows for flexible (0.8mm) lateral wall electrodes (Flex electrodes; MED-EL).

The current HEARO procedure for RACI comprises several steps of: 1) titanium fiducial screw placement 2) perop CBCT imaging, 3) pre-operative trajectory planning, 4) patient-image registration, 5) middle ear access robotic drilling till 3mm lateral from the facial nerve 6) CBCT with reference rod in the drilled trajectory to control for deviations from the planned trajectory, 7) stepwise drilling passing the facial nerve plane with electric facial nerve monitoring till access of the facial recess and 8) inner ear access robotic drilling with drilling pressure control at the round window bony overhang (cannonostomy). Upon the completion of the HEARO procedure the electrode is then inserted inside the cochlea under endoscopic guidance.

*Speaker

Pre-clinical evaluation of the full HEARO procedure including the electrode insertion and scanning evaluation was performed on ten formalin flushed temporal bone specimen were used for the study.

The Hearo procedure was then performed under IRB UZA (EAR^2OS and ARCI25 trial.gov) approval as a feasibility study in three patients and subsequently as an efficacy study ongoing for 25 patients with severe to profound sensorineural hearing loss and in which the temporal bone anatomy allowed enough space between the facial nerve and the chorda tympani for save passage of the drill.

Results

The temporal bone study ascertained the feasibility, the accuracy and the reliability of the procedure. We were able to segment all anatomical structures of interest, to measure the cochlear parameters, to plan a trajectory and to perform the inner ear access with electrode insertions. The variability of defining and accessing the different predefined targets resulted in SEM of 0.05-0.07mm.

These results allowed for the human feasibility experimental surgical CI using RACI. The results in terms of accuracy and precision and the experiences of the first patients will be presented and discussed. No adverse events were noticed and the full procedure could be performed.

Conclusion
Robotic assisted cochlear implantation is feasible in clinical setting. The procedure proves to realize the requested accuracy and precision to safely perform the procedure and form a sound platform for improving CI surgery.

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POSTER ABSTRACT

P1

Evaluation of hearing and quality of life of patients implanted with a bone-anchored prosthesis

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Abstract

Introduction :
Bone-anchored implant is a device for compensating hearing loss by direct bone conduction. The idea of these prostheses is based on the use of the bone conduction pathway to directly stimulate the healthy cochlea, bypassing the outer and middle ear.
The sound is filtered then amplified before being transmitted to the healthy cochlea.

Percutaneous systems and others with closed skin (transcutaneous) are described.

These prostheses require a surgical act for their implementation, in one or two stages, except in the case of rehabilitation by prosthesis on a flexible band, widely used in children under 5 years
of age.

Objectifs :
The aim of our work was to evaluate the hearing and the quality of life of patients with a bone-anchored prosthesis. And reporter the post-surgical complications.

Methods :
We conducted a retrospective study between 2021 and 2022 with bone-anchored hearing aids in the ENT and CCF department of the CHU ibn Sina Rabat specialty hospital between 2021 and 2022.

Results :
5 patients were answered to the quality of life questionnaires, APHAB and GHABP.

The average age of the population was 14.56 years. Four patients (44.44%) had normal contralateral hearing, 1 patient had sensorineural hearing loss (11.11%) and 4 had mixed

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hearing loss (44.44%) on the non-deployed ear.
Bone-anchored prostheses significantly improved tonal and vocal hearing. The overall average prosthetic threshold was 35.66 dB (15-67.50 dB), 31.72 dB for mixed deafness and 31.70 dB for cophosis. The average tonal prosthetic gain was 54.98 dB. Regarding free-field speech audiometry, the mean prosthetic threshold was 38.69 dB.
An improvement in the overall score of the APHAB questionnaire of 37 points was obtained (from 67% to 30%, p = 0.036). The average benefit of the prostheses was 37.05% (0-80.33). Ten postoperative complications occurred, including 6 major (3 grade 3 and 3 grade 4 from the Holgers classification). Grade 4 which required an abutment change within an average of 5 months after the initial surgery.

Conclusion :
Bone-anchored prostheses provide real comfort to the patient both in terms of hearing and quality of life. They improve understanding in noise allowing patients to follow conversations in noisy atmospheres and therefore the quality of life.

Keywords: bone, anchored implant, hearing loss, direct bone conduction, cochlea

P2

Outcomes of late cochlear implantations of prelingual deafned children

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Abstract

Objectives:
The aim of this study is to compare the speech therapy results of late implanted perlingual deaf patients
with those who benefited from an early implantation, in order to justify the place of cochlear implantation in children over 5years old and to demonstrate its benefit in the development and social
integration.
Methods:
Comparative study over a period of 11years involving 78children implanted in our department in age
over 5years old subdivide into two groups -GROUP B- between 5 and 7years old and -GROUP C- more
than 7years compared to a control group A- of children less than 5years old with a follow-up of at least
1year in postoperative. The different scores CAP APCEI SIR were used to analyze the evolution of speech
therapy.
Results:
The speech therapy results showed poor outcomes for groupC concerning APCEI, CAP scores qualitative
and quantitative sound perception compared to other groupsA and B. Despite those mediocre results
were appreciated by the parents in view of the development of the children as well as their social
integration. However, group A had average CAP and APCEI scores of more than 90% of CAPmax and
APCEImax respectively at 1year after cochlear implantation compared to a percentage increase of 80%
for groupB. Therefore, it can be concluded that even in children aged over 5years benefits from a
notable improvement in the results of auditory perception at 1year after CI, thus making it possible to

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underline the importance of cochlear implant but in patients over 5years old.
Conclusion:
The primary goal of cochlear implantation is to provide critical speech information to the child's auditory
system and brain to maximize the chances of developing spoken language. Evaluating the success of
cochlear implantation requires careful consideration of intervening variables, implantation at younger
ages and rehabilitation focused on speech and auditory skill development for social integration. Funding: None

Keywords: Late cochlear implant, Children, Prelingual, Deafness, Speech therapy

P3

Functional outcomes in cochleostomy and round window insertion technique of the cochlear implantation

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Abstract

Background: The cochlear implant can be done by means of different techniques, traditionally by Cochleostomy method and round window membrane insertion technique. Post operatively, the functional outcomes are measured by many scores more commonly by Categories of Auditory Performance (CAP) and The APCEI profile.
Objective: This study aims to study the functional outcomes in terms of speech and hearing perception skills post Implant by two different surgical techniques.

Methods: Children (n = 255) between 2 and 15 years old who had bilateral profound sensorineural hearing loss, 220 children had a round window insertion while the other 35 children had a cochleostomy insertion. The choice of the method for electrode insertion was the surgeons preference intraoperatively. 22 array electrode insertion was done.

Results: Post operatively functional outcomes were assessed subjectively by measuring CAP and APCEI scores. Both the study groups were comparable with respect to age. All the patients showed increase in their CAP and APCEI scores post-operatively, measured at 03 months, 06 months and 01 year after Cochlear Implantation. The mean CAP and APCEI scores in the two groups were comparable at 03 months, 06 months and 1 year after surgery. There was no significant difference in the speech and hearing perception skills of post implantees in the two groups; there is no difference in functional outcomes of Cochlear implantation.

Conclusion: Cochlear implantation now has proven efficacy in the rehabilitation of severe and profound deafness. The current available literature regarding the influence of different insertion methods on the degree of hearing preservation or loss is limited. As yet, there are no valid data to support any statement on the clinical superiority of either approach.
Funding: None

Keywords: Cochleostomy, Round window membrane, CAP, APCEI

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P4

BENEFIT of Cochlear implantation in children with Multiple handicap and comorbidities – evaluation and parent satisfaction

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Abstract

Background: The number of children with hearing loss with additional disabilities has increased dramatically over the past decade. However, candidacy criteria for cochlear implants have expanded to include these special cases.
Objectives : This article will review the literature regarding cochlear implant considerations in cases with cerebral palsy, in areas of family perception, cognitive and language development, communication and functional skills, auditory outcomes and quality of life outcomes.
Methods: At an interval of time ranging from march 2018 to march 2022, 5 children with complex developmental disabilities who also have hearing loss had benefit from cochlear implantation in the department of otorhinolaryngology of university hospital Mohammed VI of Marrakech. They have been assessed preimplant et 12 months post implants switch-on. Outcomes were studied and analyzed using appropriate scores such as categories of auditory performance (CAP), The APCEI-scale (Acceptation, Perception, Comprehension, oral Expression, Intelligibility) and speech intelligibility rating (SIR).
Results: The results were quite variable, but overall positive. Among our serie, 2 parents refused to participate while the remaining three parents agreed to answer our survey confirming that their children showed significant improvement postimplantation on CAP , APCEI and SIR, in term of speech perception, functional skills and quality of life.
Nevertheless, this category of children didn't reach gains achieved by their counterparts who do not have additional health concerns.
Conclusion: Despite the fact that development of hearing may be protracted for children with complex developmental disabilities, Cochlear implantation remains a beneficial and reliable milestone in the management of deafness; even for these particular cases; providing benefits in auditory, promoting development of communication and therefore encouraging social integration.
Funding : None

Keywords: evaluation and parent satisfaction.Multiple handicap and comorbidities

*Speaker

P5

Quality of life in prelingually-deafened, Late-implanted patients.

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Abstract

Background: Prelingually-deafened, Late-implanted patients braces poorer and widely variant objective results, however with the development of QoL concepts ; many authors describes a QoL improvement both for the recipients of PL-LI as their families ; defining the subjective results.
Objectives : Reevaluating and expanding cochlear implantation's indication while measuring the quality of life outcomes regarding the parent's point of view of prelingually-deafened, late-implanted patients, which are widely known to showcases a limited improvement in speech recognition.

Methods : A retrospective descriptive and analytic study to assess QoL outcomes from cochlear implantation in 64 early deafened late implanted patients, according to their parent's perspective, between January 2009 and December 2019 ; utilizing the Nottingham Pediatric Cochlear Implant Program (Nottingham University Hospital, Nottingham, United Kingdom) " Children with cochlear implantation : Parents perspective" .

Results : The most represented age interval is the 5 and 7 interval and the mean age is 10.09. There was no gender predominance, with rural origin and high school academicals level preponderance. 14 children had suffered from neonatal icterus, 8 from meningitis, 7 were the result of related marriage. The age of the first consult was meanly > 2 years old, with only 45 schooled child. Age had a significantly statistic correlation between Self-reliance and Wellbeing and happiness subscales. History of receiving aid and speech therapy has a clear correlation with Self-reliance, Wellbeing and happiness, Communication and Education. Schooling statuses, gender, age of appearance, communication mode were not correlated to any sub scale score and at the exception of Effect of implantation, all the other sub scales were intercorrelated.

Conclusion : Proper and validated QoL assessments for cochlear implantation is a most, as outcomes of cochlear implantation expands beyond audiometric performances alongside improvement of QoL.
Funding: None

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Keywords: Quality of life, Cochlear Implant, prelingually, deafened, Late, implanted patients.

P6

Evaluation of the functional results of cochlear implantation at the University Hospital Of Marrakech

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Abstract

BACKGROUND: Cochlear implants combined with early identification and management of hearing
loss are an essential tool to manage deafness, whether acquired or congenital.
OBJECTIVES: Our goal is to evaluate cochlear implants and identify factors influencing outcomes in
our practice through the study of the experience of the Otorhinolaryngology and Cervico-Facial
Surgery department at Mohammed VI University Hospital in Marrakech.
METHODS: This prospective study spanned 14 years (December 2007 to December 2021). During this time, 289 patients were implanted and followed in our program. All patients underwent
unilateral implantation, followed by regular adjustments and speech therapy. Evaluation was
conducted by the same team each month for the first six months, then every six months thereafter.
Tonal audiometry was used to evaluate audiometric gain, while APCEI profile was used to assess
speech therapy outcomes.
RESULTS: Of 289 patients, 155 were female and 134 were male with severe to profound bilateral
hearing loss; 278 were children (96 were from consanguinous relations, 42 suffered neonatal distress, 21 had an inner ear malformation, 16 had meningitis, 10 had cerebral palsy), 190 children
had pre-lingual deafness, 11 were adults. The average age for cochlear implantation was 5.74 years.
During surgery, full insertion of electrodes was achieved 274 times, with at least 75% active channels,
The average follow-up duration was 44.77 months. All patients benefited from implants with varying
interindividual results. Positive outcomes were correlated with early implantation, full insertion of

*Speaker

electrodes, significant parental involvement, and consistent speech therapy follow-up.
CONCLUSION: Cochlear implantation has revolutionized the management of profound and severe
hearing loss. It is a safe and effective tool when applied to properly selected populations, hence the
role of early screenings in newborns and small children, to allow earlier implantation, and better
results.
FUNDING: None

Keywords: coclear implantation, inner ear, speech therapy, apcei, tonal audiometry, deafness, marrakech

P7

IMPACT OF NUMBER AND INTERGRITY OF INSERTED ELECTRODES IN THE COCHLEA ON SPEECH PERFORMANCE OF PERDIATRIC COCHLEAR IMPLANTS

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Abstract

Background: speech perception and language outcomes after early cochlear implantation differ greatly from one patient to another, many factors seem to contribute to this variability, so it is necessary to determine the factor that most influences these results.
Objective: This study investigates the impact of number of inserted and active electrodes in the cochlea as recipient-dependent factors affecting the speech therapy outcome.

methods: The subjects were 101 prelingually deaf children who received unilateral Nucleus 22 Cochlear implant. We selected a sample of 25 patients of similar age (4 and 5 years old) with idiopathic cause of deafness who have benefited from proper speech therapy for 2 years or more. we have identified the number of activated electrodes from the inserted ones, then a postoperative radiograph of the cochlear electrode (Stenvers incidence) was used to identify the length of the inserted cochlear array, the speech performance was evaluated using the APCEI and the CAP score.

Results: All 25 patients had all 22 electrodes fully inserted, and we had 4 patient groups of active electrodes: 22/22, 20/22, 19/22 and 17/22, the best speech outcome was observed in the first group, and in patients with an insertion length between 17-25 mm, the worst results were observed in group 4 and in patients with an insertion length exceeding 25 mm.

Conclusion: Cochlear implant's electrode array's depth insertion and the number of active electrodes does influence postoperative speech outcomes. underscoring the importance of the placement of the electrode array and the control of its length insertion during surgery.
Funding: none

Keywords: cochlear implant, prelingual deafness, active electrode, inserted electrode, speech thearpy, pediatric

*Speaker

P8

Complications of cochlear implant surgery: Experience of the ENT Department of University Hospital Mohammed VI Marrakech Morocco

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Abstract

Background: Since its advent, several publications have described the complications of cochlear implantation; most of them classify these complications into minor and major ones. **Objectives:** The objective of this study is to analyze the complications in our series of implanted adult and pediatric patients and to report our routes of management.

Methods: We thus, conducted a retrospective study reviewing complications of cochlear implantation performed in the ENT department of university hospital Mohammed VI Marrakech Morocco, from January 2010 to December 2022.

Results: The average age of implantation was 5.15 years, 51,5% were girls. 25 postoperative complications were reported in our series, classified as either minor in 76 % of the cases; where management is conservative, and major for 24%; requiring hospital management or even surgical revision.

Conclusion: Cochlear implantation remains a relatively safe procedure; mainly responsible for minor complications due to the progress of the surgical technique and the expertise of the surgeon.
Funding: None

Keywords: cochlear implant, major/minor complications

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P9

Inner ear malformation : limit of cochlear implantation

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Abstract

Background : : Inner ear defects result from an interruption in the development of the inner
ear during the first trimester of fetal development. They are responsible for 20% of congenital sensorineural hearing loss, which is most often bilateral and profound. Their diagnosis is radiological, and relies on the CT-MRI pair. The identification of malformed structures allows the choice of therapeutic modalities.
Objectives : to investigate and learn about the limitations of cochlear implantation in children with inner ear defects
Methods : A retrospective study was conducted on 120 children with profound sensorineural hearing loss who were candidates for cochlear implantation between September 2021 and May 2022. The preoperative evaluations were analyzed. For comparative outcome analysis, children with EIM were matched and compared to children with normal inner ear who had received implants.
Results : 4 children, 3 girls and 1 boy out of 120 children with profound sensorineural deafness were candidates for cochlear implantation; with an average age of 4 years, the candidates benefited from a preoperative assessment: auditory evoked potentials, CT and MRI of the rocks.
Of which 4 children showed incomplete partition of the Cochlea type III, Complete Labyrinthine Aplasia, Cochlear Hypoplasia CH-II and agenesis of the corpus callosum on brain
MRI, considered as a contraindication for IC. Conclusion : Cochlear implantation on inner ear malformation is considered a difficult
surgical situation wich success in remains compromised.
Detailed preoperative assessment including audiometry, CT of the rocks, MRI are primordial.
Universal classification of inner ear malformations: surgeons, radiologists, audiologists, speech therapists.
Funding : None

Keywords: inner esr malformation

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P10

Cochlear Implantation in patient with Dandy-walker Syndrome

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Abstract

Introduction:
Dandy Walker Syndrome is the most frequent cerebral malformation, it's defined as a congenital abnormality in the central nervous system, characterized by a deficiency in the development of middle cerebellar structures, cystic dilatation of the posterior pit communicating with the fourth ventricle and upward shift of the transverse sinuses, tentorium and dyes. In addition to these classical findings, the Dandy-Walker malformation is characterized by other abnormalities and malformations of the central nervous system (CNS) including agenesis of the corpus callosum, heterotopia, occipital meningocele, visual deficits and epilepsy. Neurogenetic and imaging examinations have led to a better understanding of this malformation.

Bilateral sensorineural deafness can be part of the clinical picture of the syndrome and cochlear implantation can be proposed for profound bilateral deafness.

Objectives:

To report a case of a little child; 5 years old with a diagnosis of this syndrome and bilateral hearing loss underwent cochlear implant surgery under general anesthesia, after no response to the use of hearing aids.

Case report:

A 5-year-old child with no history of neonatal distress was referred to Our Otolaryngological Department by her treating pediatrician; with a diagnosis of "Dandy-Walker syndrome" in order of an evaluation for bilateral hearing loss with delayed language acquisition. The child had no response to the use of hearing aids.

The diagnosis of prelingual deafness was confirmed by Auditory evoked potential (AEP); The CT scan of the Temporal Bone has not revealed any malformation of the inner ear or the internal Acoustic Meatus; and the MRI showed the Dandy Walker-type cerebellar malformations.

A Left unilateral cochlear implantation was performed under general anesthesia. The implant was activated 2months after surgery with excellent sound perception at the time of activation

*Speaker

Conclusion : The field of cochlear implants is growing rapidly. We believe that the presence of Dandy-Walker syndrome cannot be considered as a contraindication to the performance of cochlear implant surgery, and there were no surgical complications due to neurological disorders with very favorable results for the patient. The implantation results bring impact on quality of life of patients while providing better social integration.

Keywords: Dandy, walker, Cochlear Implantation, hearing loss

P11

Cochlear implantation in children with Effusion otitis media

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Abstract

Objective:
The aim of this study was to report the therapeutic methods in children with Effusion otitis media (EOM) before surgery, to assess the surgical difficulties of CI, and the post-operative complications.

Methods:

A retrospective chart review of patients from a large cochlear implant program was conducted in ENT- head and neck surgery department, Arrazi Hospital, University Hospital of Marrakech, Morocco.

We carried out a comparative study between group A candidates operated with EOM and group B candidates operated without OME, and we reported: age, treatment modalities, computerized tomography CT scans, surgical finding and difficulties, postoperative complications

Results:

278 pediatric patients were implanted unilaterally during January 2008 to December 2021. 40 patients have benefited from CI with OME (group A) after failure of regular medical treatment and 238 patients operated without OME (group B).

The average age in group A and B successively 3,3 and 4,5 years. CT scan in patients with effusion had excessively an opacification of middle ear, poorly pneumatized mastoid and high sclerotic facial recess compared to patients without effusion, the difference was statistically significant ($p< 0.001$).

In group A we noticed excessive bleeding, mastoid granulations tissu during mastoidectomy, a congested and bleeding muscosa makes the dissection of the mucosa in front of the round window more difficult compared to patients without effusion, the difference was statistically significant ($p< 0.001$).

The Follow-up found some transient complications; group A: 4 case of mastoiditis; 2 case of

*Speaker

wound infection with released sutures and 2 cases of acute otitis media. In group B: we had 1 case of meningitis, 1 case of House-Brackmann grade III facial palsy on day 1 postoperative was found with intraoperative exposure of facial nerve, 3 cases of retro-auricular hematoma, 3 cases of wound infection with released sutures. And 5 cases of acute otitis media.

There was no significant difference in the speech results and hearing perception skills in long-term speech therapy (P0.001)

Conclusion:
Current results revealed that CI is generally safe in children with OME and that delaying the implantation process might be unnecessary.

Keywords: cochlear implant, effusion otitis media

P12

CHALLEGENGES OF COCHLEAR IMPLANTATION IN INNER EAR MALFORMATIONS

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Abstract

Background : Malformation of the inner ear (IE) represents 5 to 20% of congenital neurosensory deafness and only 20% have a radiological expression.
Objective : The focus of our study is to show through a literature review and a series of our department service the classification of malformation of the inner ear, the surgical difficulties, the perioperative incidents, the surgical approach and finally the results of the speech therapy.

Materials and methods: This is a retrospective study of 21 cases of malformations of the Inner Ear (A total of 348 cochlear implantation) Implantations are done at the ENT department of Mohammed VI University Hospital of Marrakech, over a period of 14 years (from January 2007 to December 2022).

Results: All children were suffering from a prelingual Deafness their average age (4 years), Consanguinity (7 cases), Genetic deafness (5 cases).
Patients were classified according to their malformation types, 4 cases of Mondini malformation, 11 cases of Enlarged Vestibular Aqueduct,1 case of absence the Semicircular External Canal, 1 case of Cochlear Nerve Hypoplasia, 1 case Enlargement of the Cochlear Aqueduct and 3 cases of Cochlear aperture abnormalities.
The perioperative findings reveals , 5 cases Prolapse 3rd portion of the facial nerve and a difficult access to the RW (high orientation) of which 2 cases requiring a Cochleostomy. 6 Geyser ear cases requiring head elevation and temporal muscle fascia.
Insertion was complete in 19 cases, 2 cases of incomplete insertion.
Speech therapy evaluation was carried out 1 year after cochlear implantation (APCEI score) in comparison to a control group (same age group) No significant difference between the 2 groups. But most malformations are minor and the results are global.
Conclusion: Cochlear malformation of the inner ear does not contraindicate cochlear implantation. However, it represents a serious challenge for surgeons. Also, advancement of speech are more likely similar for children with and without inner ear malformation.
Source of funding: None

Keywords: COCHLEAR IMPLANTATION, MALFORMATION, INNER EAR

*Speaker

P13

cochlear reimplantation : surgical technique and results

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Abstract

Background : Retrospective analysis of consecutive clinical series.
Objective: A small number of cochlear implant recipients require reimplantation. This study describes the causes of failure, surgical technique, and hearing outcomes in a consecutive series of 10 patients undergoing reimplantation . We hypothesize that reimplantation is safe and that hearing results are at least as good as those measured following primary implantation.

Methods: Chart analysis of all consecutive cochlear implantation operations performed at university hospital center Mohammed VI of Marrakech revealed 10 patients who received a second reimplantation. 2 patients were operated in our center while the 8 others were recruited by other structures ; Main outcomes of the initial procedure were compared with those of the reimplantation, including electrode insertion length and audiometric results. In addition, cause of failure and relevant surgical findings are described.

Results: There were no surgical complications after reimplantation surgery. Device failure was the most frequent cause for reimplantation. Time between initial implantation and failure ranged from 0 to 46 months . Common intraoperative findings include mastoid fibrosis, bone growth at the cochleostomy, and skin flap breakdown. Following reimplantation, mean length of insertion, number of channels actively programmed, and speech recognition scores were at least as good as findings before initial implant failure.
Conclusion: Cochlear implant reimplantation is safe and effective.

Keywords: cochlear reimplantation

*Speaker

P14

Cochlear implantation for neurosensory hearing loss : experience of the ENT department at the CHU Mohammed VI in Oujda

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Abstract

Introduction: Cochlear implantation has revolutionized the management of neurosensory hearing loss, particularly profound or severe cases, and the ENT department at CHU Mohammed VI in Oujda began performing this type of intervention in 2015 and has adopted a diagnostic and therapeutic strategy adapted to this type of hearing loss.

Objective: To study the epidemiological, clinical, therapeutic, and follow-up profiles of patients operated on by cochlear implantation for neurosensory hearing loss in the ENT department in Oujda.

Materials and methods: We conducted an 8-year retrospective study and collected 36 cases of patients operated on by cochlear implantation for neurosensory hearing loss in the ENT department at CHU Oujda.

Results: The average age of our series ranged from 3 years to 42 years, with an average age of 5.3 years, and we were initially interested in the pediatric population who needed to acquire normal language and avoid hearing impairment. The male-to-female ratio was 1.23 among patients who mainly had a history of ToRSCH materno-fetal infection, 2 cases of meningitis, and a history of medication use. The average diagnostic delay was 8 months, and the average cochlear implantation time was 1.7 years. The auditory functional assessment of these patients included tonal and vocal audiometry if possible, the study of PEA and OEA, in combination with a pre-implantation morphological assessment consisting of CT scans of the temporal bones, brain MRI centered on the cerebellopontine angle, as well as speech therapy evaluation as part of a comprehensive evaluation. The etiologies are not always clear and are dominated by Mondini malformation, genetic hearing loss, and environmental hearing loss related to acute fetal distress or materno-fetal infection. The average duration of the intervention was 2 hours and 7 minutes with mastoidectomy, posterior tympanotomy, and electrode implantation in the cochlea without postoperative complications.

Discussion: Cochlear implantation has made the impossible possible in the treatment of

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profound hearing loss in general, and especially neurosensory hearing loss, which is the most common type in a population of language acquisition age. However, this is a financially heavy management and requires the participation of several stakeholders as well as family involvement at every stage of the process. Subsequently, the indication has been expanded to the adult and older population with perception hearing loss related to presbycusis or other causes. For this reason, scientific societies have well codified the indications of cochlear implants in profound and severe neurosensory hearing loss. Our department serves the population of the Oriental region in Morocco and has become an expert in cochlear implantation for this type of hearing loss, and the results are satisfactory and encouraging for further developing this practice.

Conclusion: Cochlear implantation is not a last resort treatment for neurosensory hearing loss, but it is the main option in the management of this type of hearing loss and can be proposed from the outset in cases of profound hearing loss according to specific recommendations.

Keywords: neurosensory hearing loss, PEA, cerebellopontine angle MRI, cochlear implantation.

P15

Predicting round window accessibility during cochlear implant surgery based on pre-operative imaging of the temporal bone.

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Abstract

Background: Clear identification of the round window (RW) through the facial recess, is a fundamental and key surgical step for successful cochlear implantation (CI) surgery, via the standard posterior tympanotomy approach, which may be very challenging in some cases. Therefore, surgeons should be able to predict RW accessibility pre-operatively.
Objectives: To determine if there are potential pre-operative imaging markers that could help predict the surgical accessibility of the RW via the facial recess during CI surgery, using high resolution computed tomography (HRCT).

Materials and Methods: We retrospectively reviewed preoperative HRCT scans of 142 patients who underwent CI surgery in our ENT Head and Neck surgery department. Surgical accessibility of the RW was assessed according to 2 methods, similar to the ones introduced by Mandour et al and Elzayat et al.

Pre-operative imaging data was then compared to the actual surgical accessibility of the RW by reviewing surgical notes, and video recordings.

Results: There was a strong statistically significant correlation between imaging data and intraoperative findings. Sensitivity (Se) and Specificity (Sp) of Mandour's method, in the prediction of RW surgical accessibility in our series were **56.3%**and **96.4%**respectively. Positive predictive value (PPV) and negative predictive value (NPV) were **81.8%**and **88.3%**respectively. On the other hand, Sensitivity (Se) and Specificity (Sp) of Elzayat's method were **50%**and **94.5%**respectively. Positive predictive value (PPV) and negative predictive value (NPV) were **72.2%**and **86.6%**respectively. Combining both methods showed an increase in sensitivity levels (**Se= 71.9%**), and better correlation with surgical findings, allowing us to predict difficult surgical access more accurately.

Conclusion: These 2 methods are both simple and reliable tools that can be used to anticipate difficult RW access and poor surgical exposure through the facial recess during CI surgery.
Funding:None.

Keywords: Cochlear implant, Round window, Temporal bone imaging

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P16

Cochlear implantation and post-meningitic deafness.

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Abstract

Background:
Cochlear implantation surgery for patients with severe to profound sensorineural hearing loss caused by bacterial meningitis can be very challenging in some cases due to variable amount of fibrosis and ossification of the fluid spaces of the cochlea.

Objectives: To evaluate outcomes and challenges of cochlear implantation surgery in patients with post-meningitic deafness.

Materials and methods: We retrospectively reviewed medical records of **340** patients with severe to profound bilateral sensorineural hearing loss, who underwent cochlear implantation surgery at our ENT Head and Neck surgery department.

Results: a total of **11** patients with post-meningitic hearing loss was identified, **7** children and **4** adults with a mean age of **5.25** year ranging from **3** to **27** years old. Hearing loss was prelingual in **6** cases and post-lingual in the remaining **5** cases. Cochlear ossification was encountered intraoperatively in **9** patients, **6** of which had evidence of decreased cochlear patency on the pre-operative CT scan. However, it was missed by CT in the remaining **3** cases and only identified by MRI. Surgical management consisted of drilling a tunnel through the bony obstruction into the scala tympani of the basal turn to expose an adequate lumen to permit safe electrode insertion. Complete electrode insertion was achieved in **6** cases, the **3** others had partial electrode insertion confirmed on post-operative Stenver's view X-ray. No post-operative complication was noted and all patients received close and consistent follow-up after hospital discharge.

Mean APCEI score for speech perception outcomes was 15.45 ranging from 13 to 19, in this group of patients.
Conclusion: Cochlear ossification is not a contraindication for cochlear implantation surgery. Patients with severe to profound sensorineural post-meningitic hearing loss should be referred quickly for cochlear implantation candidacy evaluation before onset of extensive fibrosis and ossification.

Keywords: Cochlear implantation bacterial meningitis Cochlear ossification

*Speaker

P17

Post-Meningitis Deafness: Experience of the ENT Department at HSR (2019-2021)

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Abstract

Introduction:
Bacterial meningitis is the most common etiology of acquired sensorineural hearing loss in children. This infection can cause deafness by peripheral or central hearing impairment. Bacterial meningitis infection creates lesions by immune reaction, inflammation, ischemia, or cerebral edema. For ENT physicians, ossification of the organ of Corti is the lesion to be feared after bacterial meningitis.

The objective of our work is to determine the diagnostic means of a post-meningitis deafness, the assessments to be carried out and to objectify the clinical and radiological aspects as well as the various therapeutic means.

Materials and Methods:

This is a retrospective study over a period of 2 years from 2019 to 2021 on 14 cases of post meningitis deafness, collected in the ENT-CCF department at the Hospital of Specialties in Rabat.

Results:

The mean age of our patients was 6.92 years with extremes ranging from 2 years to 17 years. The gender distribution was 9F/5H. The delay between the meningitis and the onset of deafness was 5 months ranging from 3 days to 1 year. The causative germ was pneumococcus in the majority of cases. The onset of deafness was abrupt in 5 patients and progressive in 9 patients. Pure tone audiometry was performed in children older than 5 years and auditory evoked potentials were performed in all patients, which allowed confirmation of the deafness. CT scans and magnetic resonance imaging were performed in 10 of our patients and showed ossification of the cochlea unilaterally or bilaterally in 4 patients. Six patients of our serie benefited from a cochlear implantation with good evolution.

Conclusion:
Sensorineural hearing loss can occur immediately or several months after bacterial meningitis, regardless of the germ, and prompts age-appropriate audiometric monitoring. An auditory evoked potentials measurement can confirm the audiometric findings. When severe or progressive deafness is diagnosed, a CT scan and MRI should be performed as a matter of urgency to detect cochlear ossification, which will determine the urgency of cochlear implantation.

Keywords: Post, meningits deafness

*Speaker

P18

Hearing aids in flight personnel

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Abstract

INTRODUCTION:

The aeronautical environment is a very noisy environment which can cause deafness, preventing the good comprehension of radio instructions and thus compromising the safety of flights.

The aim of this work is to review the different hearing aids currently available and their possible applications in aeronautics.

DISCUSSION:

Deafness in the aviator is not rare because the aeronautical environment is a harmful environment for the auditory system because of the ambient noise and because of the exposure to pressure variations. The aviator is led to protect himself by using noise attenuators which are either passive protection or active protection (Active Noise Reduction).

But once the deafness is installed, is it possible to wear a hearing aid? And if so, which one to choose? To answer this question, we will study the different hearing aids and their possible applications in aviation.

Conventional hearing aids, middle ear implants, bone conduction hearing aids (BAHA), cochlear implants and brainstem implants are the different hearing aids analysed.

CONCLUSION:

It is important to point out the important role of prevention of noise pollution and barotrauma.

The appearance of hearing loss is not synonymous with incapacity. A derogation, after carrying out intelligibility tests in noise with the equipment, remains possible, especially in civil aviation.

Keywords: aides auditives, personnel navigant

*Speaker

P19

Gene therapy for hearing loss: a systematic review

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Abstract

Background: Gene therapy for hearing loss is a promising and rapidly evolving research topic with the ultimate perspective of clinical implementation. Its potential might be considerable as the only treatment restoring natural hearing with functional superiority over current options in a potentially large group of deafness patients.
Objectives: To summarize the results of published murine gene therapy trials with local administration of gene-specific gene therapy, and to extract determinants for success by comparing their approaches.

Methods: In this systematic review, we performed a PubMed search from inception to January 8th, 2023, and hand-searched for additional reports. Hearing was evaluated as the primary outcome, whereas microscopic inner ear evaluation was a secondary outcome. Relevant methodological characteristics were collected as well.

Results: In total, 44 publications could be extracted, in which therapy for 21 different deafness genes was described. The majority showed improvement in cochlear structure and hearing after gene therapy, although sometimes modest, temporary or only at young mural age reflecting the prenatal period in humans regarding auditory maturation. Transduction levels and hearing outcomes seem related to the timing of injection, used vector and surgical technique. Recent progress has been made, especially in vector design and approaches for genes larger than AAV capacity, leading to improved transduction and consequent hearing outcome. At least two genes are very promising given their good results in adult mouse injections: reversibility of existing profound hearing loss in *OTOF* and delayed progression of hearing loss in the dominant model of *TMC1*.

Conclusions: Genes resulting in congenital hearing loss without initial structural damage or genes provoking progressive hearing loss seem most promising towards gene therapy for hearing loss, as they enable a strategic window for timely administration. Otoferlin gene therapy reached the phase of human clinical trials and more will probably follow.
Funding: The authors received no financial support for the research or authorship of this work.

Keywords: Gene therapy, otoferlin, systematic review

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P20

Design and validation of mutant allele-specific antisense oligonucleotides for the future treatment of adult-onset hearing loss type DFNA9

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Abstract

BACKGROUND: We estimate that > 1500 individuals in the Netherlands and Belgium carry the c.151C> T mutation in *COCH* resulting in DFNA9. DFNA9 has a highly predictable disease course, with an average onset of progressive hearing loss around the age of 30-35. Therefore, the Dutch/Belgian DFNA9 population presents us with a unique opportunity to bridge the gap between pre-clinical and clinical research.
METHODS: The dominant-negative and/or gain-of-function disease mechanism of DFNA9 indicates that the allele-specific degradation of mutant *COCH* transcripts can alleviate or remove the burden caused by the formation of cytotoxic mutant cochlin proteins. Following our success with antisense oligonucleotides (ASOs) for Usher syndrome, we designed gapmer ASOs to induce the specific breakdown of c.151C> T mutant *COCH* transcripts. We employed different in-vitro models and ASO chemistries to identify the most efficacious and mutant allele-specific ASO for future use in DFNA9 patients.

RESULTS: We initially compared the efficacy of 7 ASOs for their ability to lower mutant *COCH* transcript levels in a transgenic cellular model. The length and chemical composition of the best-performing ASO was altered to further optimize the ASO. We investigated molecular efficacy and allele-specificity both on mRNA and protein levels.

CONCLUSION and PERSPECTIVES: ASOs offer a unique platform for the future treatment of DFNA9 and other hearing loss disorders. Molecular efficacy and targeting-specificity of ASOs can be improved by introducing chemical modifications, which is a key advantage of ASO technology over other RNA-targeting approaches. Currently, we are taking the first steps to assess ASO efficacy in a humanized DFNA9 mouse model and patient-derived inner ear organoids. The proven clinical safety of ASOs for several other disorders allow for a relatively swift translation towards clinical studies after in-vivo proof-of-concept has been obtained.

Keywords: DFNA9, antisense oligonucleotides, allele, specific therapy, knock, down

*Speaker

P21

Engineering Efferent Feedback to Protect Hearing

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Abstract

Cholinergic brainstem neurons innervate the adult cochlea to inhibit mechanosensory outer hair cells. These efferent neurons are themselves driven by sound and so constitute a negative feedback loop to regulate cochlear sensitivity. Efferent cholinergic feedback also provides protection against acoustic trauma. That protection is absent from AChR null mice (lacking the ligand-binding α9 subunit) and is stronger in knockin mice expressing a gain-of-function point mutation (α9L9'T) of the hair cell's AChR. The present work uses viral transduction to introduce α9L9'T into the cochlea of α9-null mice to restore acoustic prophylaxis to restore efferent protection. Expression of the transgene was visualized with a fluorophore-conjugated Conus peptide (Cy3 RgIA-5727) a potent and highly selective antagonist of α9-containing AChRs. Viral transduction of α9L9'T into α9-null mice improved resistance to acoustic trauma. Protection was seen for acute noise-induced hearing loss, and to a lesser extent for age-related hearing loss (4-8 month old C57Bl/6 mice). Gene therapy to strengthen efferent cochlear feedback is a general strategy that would be complementary to ear coverings, hearing aids, single gene repair or drug therapy treatment. Support was provided by the National Institute on Deafness and Other Communication Disorders, grants R01 DC001508 (P.A.F., A.B.E.) and R01DC017620 (A.L.), and the David M. Rubenstein Fund for Hearing Research and Professorship (P.A.F.).

Keywords: efferent, alpha9, hair cells, nicotinic, acetylcholine

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P22

CRISPR-Cas9 In Vivo Gene Editing of Otof in postnatal Mouse Auditory Hair Cells

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Abstract

Background:
With more than 220 mutations, the *OTOF* gene (DFNB9), encoding otoferlin, is the major cause of non-syndromic recessive auditory neuropathy (synaptopathy) spectrum disorder. Otoferlin is essential for hair cell synaptic transmission but it is also reported to be essential for the maintenance of the ribbon synapses by mechanisms that remain unknown. To decipher the role of otoferlin in this later process we created a mouse model in which the transmembrane domain of otoferlin was specifically targeted using CRISPR-Cas9 technology *in vivo*.

Methods:

H11LSL-Cas9 CRISPR/Cas9 knock-in mice, with Cre recombinase-dependent expression of *cas9*, were crossed with *Myo15-Cre+/+* mice (Myo15atm1.1(cre)Ugds) to obtain offspring mice with a specific cas9 expression in hair cells. In these anesthetized P1–P3 offspring mice, a recombinant adeno-associated virus (AAV2/8) carrying a sequence encoding for otoferlin-TMD specific gRNAs was microinjected in the cochlea through the round window membrane.

Results:

H11LSL-Cas9 CRISPR/Cas9-*Myo15-Cre+/-* mice injected with AAV containing *Otof*-TMD-specific gRNAs displayed a mean increase of 35 dB in tone and click ABR thesholds as compared to control mice ($p< 0.001$) while DPOAEs remained normal. Remarkably, in these *Otof*-gRNAs injected mice, we found a mosaic decrease in the otoferlin expression in IHCs along the cochlear partition. We could establish a good correlation between the protein expression level of otoferlin and the number of synaptic ribbons per IHCs ($r=0.76$ $p< 0.001$). The size of the IHCs were also positively correlated to the level of otoferlin expression ($r=0.59$ $p< 0.01$).
Conclusion: We demonstrate as a proof of concept that CRISPR-Cas9 technology can work in vivo. Using this technology we could down modulate the expression level of otoferlin in postnatal hair cells and show that this protein is indeed essential for the maintenance of functional synaptic ribbons. This technique could possibly be used to treat cochlear synaptopathies associated with semi-dominant heterozygous p.R1939Q mutations of OTOF.

Keywords: Synaptopathy, Ribbon synapses, Otoferlin, Inner hair cells

*Speaker

P23

Dual Vector Gene Therapy for DFNB16 Hearing Loss

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Abstract

Hearing loss (HL) affects an estimated 430 million people worldwide, with a significant fraction due to genetic mutations. The second most common form of genetic HL results from mutations in the *STRC* gene, which encodes the protein stereocilin. Stereocilin is a key protein required to couple outer hair cell bundles to the tectorial membrane and maintain cohesive hair bundle stereocilia. *STRC* mutations cause progressive, mild/moderate autosomal recessive HL (DFNB16). Based on our analysis of the heterozygous carrier frequency of 1.8% in a cohort of ~1,200 normal hearing subjects, we estimate that ~2.3 million patients worldwide may carry biallelic pathogenic *STRC* mutations and suffer from DFNB16.
To address DFNB16 hearing loss, we generated a mouse model with the *Strc* gene disrupted. We developed a gene therapy approach to address hearing loss in the DFNB16 mouse model by replacing defective stereocilin in OHCs. To achieve this, we used synthetic dual AAV9-PHP.B vectors to deliver the split *Strc* coding sequence into the inner ears of *Strc*Δ/Δ mice. Four weeks following treatment, we observed a significant recovery of STRC expression in targeted OHCs, proper STRC localization at the tips of OHC bundles and recovery of OHC bundle morphology. We found that recombination of full-length STRC led to significant hearing recovery at four weeks of age, in some cases close to wild-type levels. To translate our novel dual vector gene therapy strategy for use in humans, we generated iPSC-derived human inner ear organoids that carry a recessive loss-of-function mutation in the *STRC* gene. A CRISPR-Cas9 approach was used to disrupt the *STRC* coding sequence in the parental iPSC line. Organoids generated from iPSCs lacking *STRC* expression bear normal shape hair cell-like structures (Myo7a/Phalloidin positive) and develop according to standard protocols. Our data suggest that STRC KO iPSCs-derived organoids can be a model for *in vitro* translational development of dual vector gene therapy for treatment of DFNB16 in humans cells *in vitro*.
Sources of funding: Translational Research Program Pilot Grant BCH, Rosamund Stone Zander Translational Neuroscience Center Pilot Research Grant

Keywords: hair cell, gene therapy, stereocilin, STRC, dual vector

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P24

Developing Digital Biomarkers for Auditory and Vestibular Phenotyping in Clinical Trials

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Abstract

Background: The development of therapeutics for hearing and balance has been a historical challenge. Commonly used outcome measures for hearing loss and vestibular dysfunction have several limitations, including time-consuming and costly diagnostic testing. Furthermore, subjective questionnaires may not reflect actual disability and may be confounded by neurocognitive impairment. Improved auditory and vestibular phenotyping is critical to enable large-scale natural history studies and the success of future clinical trials.
Objectives: 1) Provide an overview of Regeneron's clinical translational work to identify enabling digital tools and resources in the field of Auditory Science. This includes identifying auditory and vestibular concepts of interest and corresponding endpoints. **2)** Identify existing clinically meaningful outcomes of auditory and vestibular health, and quantitative digital endpoints which can be used to measure the natural history of disease as well as the effect of treatment with greater precision, thereby reducing sample size, cost of studies, and patient burden. **3)** Identify areas where novel digital endpoint development is needed to adequately monitor disease progression and treatment effects.

Methods: A thorough landscaping of the literature and digital health technologies relevant for auditory and/or vestibular assessment was conducted to identify areas of opportunity. Auditory-related data from two large-scale observational studies funded by the National Institutes of Health were also explored.

Conclusions: Digital health technologies have the potential to enhance what is known about auditory and vestibular disease progression, and to provide enormous opportunity to address the unmet need for interventions for various forms of these diseases. These technologies can enable more frequent evaluation, greater diversity in clinical trial populations with a more decentralized approach, and lower burden on patients and Sponsors. In order to address critical challenges in the field of Auditory Science, innovative development is warranted.

Keywords: digital biomarkers, phenotyping tools, auditory, clinical trials, digital endpoints

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P25

From Big Data to Gene Therapy - Precision Medicine for Deafness

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Abstract

Precision medicine, a rapidly developing field that uses data-driven approaches, offers new hope for people with deafness. This approach provides the opportunity for early diagnosis and precise treatments for individual patients based on their own unique genetic profile. Precision medicine has become increasingly crucial for hearing loss as it affects millions of people worldwide and has been shown to have major consequences at the social and psychological levels in children and adults. Therefore, determining the genetic background is fundamental for early clinical management, risk assessment, and developing personalized treatments. To date, over 150 genes have been identified to be associated with deafness, however, it is estimated that about half of the inherited deafness cases in the Israeli Jewish and Palestinian Arab populations remain unsolved. To address this issue, a large-scale study is being conducted on the hearing-impaired population in Israel using the KSM TipaBiobank. Next-generation sequencing (NGS) is being performed on 1200 adult deaf individuals from the Biobank, and pathogenic variants are being evaluated to determine genotype-phenotype-ethnicity correlations. Personalized genetic counseling is provided based on the identified variant, and novel variants are being functionally characterized in the lab using knock-in mouse models by in-vitro cell culture assays and CRISPR/Cas9 technology. Next, gene therapy experiments are performed, using different tools to rescue both auditory and vestibular functions in mouse models for deafness, with the perspective of treating human deafness in the future. The combination of gene therapy and precision medicine has great potential to revolutionize healthcare and provide personalized treatments for individuals with genetic hearing loss. Research funded by the Israel Precision Medicine Partnership Program 3499/19

Keywords: Big data, genetics hearing loss, gene therapy, high, throughput sequencing

*Speaker

P26

GJB2 AND LRTOMT VARIANTS ASSOCIATED WITH NON-SYNDROMIC DEAFNESSIN MAURITANIAN FAMILIES

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Abstract

Context: Although hereditary deafness is common in Mauritania due to the high rate of consanguinity, genetic data on this disease are still limited in our population.
Objective: The purpose of this study was to assess the prevalence of *GJB2* and *LRTOMT* variants in a cohort of children affected with congenital deafness recruited in two reference centers for hearing-impaired children in Nouakchott/Mauritania.

Methods: Using target Sanger sequencing, we screened regions in *GJB2* exon 2 and *LRTOMT* exon 7, respectively in 152 unrelated Mauritanian children with congenital deafness. 3D structure/function of the Protein encoded by *LRTOMT* was explored by UCSF chimera.

Résultats: Deux variantes pathogènes de *GJB2* (c.del35G et la variante faux-sens c.94C> T p.Arg32Cys avec une fréquence allèle de 4,6 % et 4,9 %, respectivement) ont été identifiées. Dans le gène *LRTOMT*, une nouvelle variante faux-sens biallélique prédite pathogène (c.179T> C;p.Leu60Pro) avec une fréquence allèle (2,6%) a été trouvée à l'état homozygote dans quatre familles non apparentées. L'exploration de la structure 3D de la protéine codée de cette variante a révélé la perturbation d'une hélice α organisée (dans la structure protéique normale) en une conformation aléatoire. La pose précoce d'un implant cochléaire semblait améliorer la capacité auditive du patient porteur de la variante biallélique.
Conclusion: Nous avons identifié des variantes de *GJB2* et *LRTOMT* probablement associées à la surdité congénitale dans la population mauritanienne. Les résultats ont souligné l'importance d'un dépistage génétique dans le contexte d'un diagnostic moléculaire précis

*Speaker

de la déficience auditive. Le dépistage génétique pourrait être optimisé en incluant d'autres gènes candidats décrits dans notre région. Jusqu'à présent, 14 variantes pathogènes ont été détectées dans l'exon 7 du *LRTOMT*. À l'instar des premiers essais de thérapie génique chez la souris pour *GJB2*, il serait raisonnable d'envisager une approche de thérapie génique pour prévenir la déficience auditive chez les patients porteurs d'une variante de l'exon 7 du *LRTOMT*.

Keywords: Mauritania, Hearing loss, GJB2, LRTOMT, Mutation

P27

Genetic Spectrum of Syndromic and Non-Syndromic Hearing Loss in Moroccan Families

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Abstract

Morocco has a high prevalence of consanguineous marriages, so heterogeneous diseases such as hearing loss are more common. Cases of deafness in Morocco are estimated at over 150,000. The exact proportion of people in Morocco suffering from a pronounced loss of hearing remains difficult to estimate due to the lack of a national registration database.
In this sense, the Genomic and Human Genetics Laboratory of the Pasteur Institute of Morocco is studying the genetic causes of deafness in the Moroccan population since 2002. Our research project's objective is to determine the spectrum of mutations and genes responsible for deafness in Moroccan patients in accordance with this vision.

Among the 318 families Moroccan recruited, 257 families had a genetic diagnostic using different strategies from linkage analysis to next-generation sequencing. Recent results of exome-sequencing, have achieved significant success in identifying possible pathogens in deaf Moroccan families. We present here an overview of the genetic profile of these families.

Of the 257 families included in our cohort, 32 % were carrying *GJB2* mutations. With 82 families harboring one or two of the 10 *GJB2* identified variants, *GJB2* represents the primary cause of deafness in Morocco. The *LRTOMT* gene is then the second most common gene with 7,4 % of NSHL cases. Besides those two genes, 46 others have been identified and confirmed among the remaining families with isolated or syndromic hearing loss. Among the many syndromes that have been identified, Usher syndrome is the most prevalent with 30 families and 6 genes with half of the cases due to variants in *MYO7A*. Other characterized syndromes include the Waardenburg, Alport, and 3MC syndromes.
In conclusion, the genetic evaluation of our patients using diverse techniques has shown it undoubtful necessity for the better understanding and evaluation of HL in the Moroccan population.

Keywords: hereditary hearing loss, genetic testing, moroccan population

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P28

Whole genome sequencing and the non-coding genome in deafness

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Abstract

Hearing loss is the most common sensory deficit in humans and the most common disorder discovered by newborn screening programs, affecting approximately 1:500 newborns. Genetic variants account for 40-60% of cases, depending on the population. While over 120 deafness genes have been discovered, nearly half of the cases are unsolved. Anecdotal reports on hearing loss caused by variants affecting non-coding regions in the genome suggest more cases could be solved by studying these regions systematically. We propose to combine whole-genome sequencing with molecular characterization of non-coding regulatory elements, such as enhancers and promoters, to increase the diagnostic yield of hearing loss. We show examples of families in which multiple family members are affected by hearing loss, for which no causative variant could be detected by whole-exome sequencing. We have identified putative regulatory elements in the non-coding genome of the mouse by analyzing H3K27ac enrichment in the genomic vicinity of known deafness genes. Our future work will focus on interrogating the sequencing data of unsolved cases in hopes of uncovering non-coding variants that cause hearing loss.

Keywords: Genetics, WGS, Regulatory elements

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P29

ACTG1: a spectrum ranging from non-syndromic hearing impairment to polymalfomative fetal presentations

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Abstract

Background/Objectives: Pathogenic variants of *ACTG1* have been reported for 2 distinct phenotypes: Autosomal dominant isolated deafness DFNA20/26 and Baraitser-Winter syndrome 2, that associates intellectual deficiency, ocular malformations, dysmorphism, epilepsy and cerebral malformations. Surprisingly, hearing impairment is seldom associ-ated to Baraitser-Winter syndrome 2. There is a high prevalence of DFNA20/26 patients identified through gene panel sequencing presenting with isolated sensorineural hearing im-pairment of dominant transmission. DFNA20/26 usually presents as non-syndromic, pro-gressive, postlingual, hearing impairment with an onset between the first and third decade. The objective is to better characterize the phenotypes associated with *ACTG1* variants. Methods: this is a retrospective study on a French cohort of 35 patients and 2 fetuses.

Results: Most of the patients have a typical presentation of DFNA20/26. 3 patients present with developmental delay and a recognizable dysmorphism with flat face and arched eyebrows. In the 2 fetal cases we found corpus callosum and cerebral anomalies, associated to cardiac and skeletal malformations for 1 of them.

Conclusion: *ACTG1* - associated phenotype is broader than currently described. We have identified extra-auditory symptoms and a recognizable dysmorphism in a number of patients.

Keywords: ACTG1, DFNA20/26, recognizable dysmorphism

P30

Genetic of congenital bilateral sensorineural hearing loss: a preliminary prospective study

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Abstract

Background

- Sensorineural hearing loss predominates congenital hearing loss, with the causes of HL broadly divided into genetic vs. non-genetic or acquired factors. Over the past 25 years, the continual advancement of technology and accuracy of diagnostic testing has revealed genetic etiology for HL occurrences in prelingual children to be as high as 60%.

Objectives

- This study has as a purpose the diagnosis of gene GJB2 mutation in a child with profound hearing loss in order to test other family members who have progressive hearing loss or allow for treatment other affected family members at a younger age.

Methods

- This is a prospective study conducted in collaboration between ENT department and genetics department of university hospital center Med 6, and it concerned 100 patients with sensorineural hearing loss. We excluded in this study patients with syndromic sensorineural hearing loss.

Results

- The age at onset of participants ranged from 6 to 18 years. Among them, 77% experienced onset in their 1st decade. 65% of patients had a family history of deafness or come from an inbreeding marriage. As for the auditory acuity, auditory evoked potentials were performed to all candidates, and the absence of wave V in bilateral was observed in 85%. 5 of our patients had a gene GJB2 mutation.

Conclusion

- Genetic testing may provide insight into management of hearing loss itself or provide guidance of when to consider additional congenital anomalies in association with a genetic syndrome.

Funding: None

Keywords: gene GJB2, SNHL, Connexin 26

*Speaker

P31

The Tietz syndrome associated with cardiac malformation: a case report

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Abstract

Background:
Tietz syndrome is a very rare clinical entity characterized by the association of profound bilateral congenital sensorineural deafness and generalized hypopigmentation of skin, eyes, and integuments. It is an autosomal dominant syndrome due to a mutation in the melanocyte inducing transcription factor (MITF) gene. The association of a heart malformation has never been reported in this syndrome.

Objective:

With this study we aim to report the importance of deafness handicap in patients with tietz syndrome and to restore a therapeutic solution for hearing problems and cardiac malformations in order to improve the prognostic.

Case presentation: We report two cases of two cousins aged 5 years and 20 months respectively with a history of first-degree consanguineous parents. Both girls presented with diffuse hypopigmentation of the skin, blond hair, blue eyes, and bilateral diffuse retinal hypopigmentation at ocular fundus exam. Bilateral profound sensorineural hearing loss was confirmed by auditory brainstem response in both cases. Echocardiography revealed a cardiac malformation such as interventricular communication in the older cousin and interatrial communication in the younger cousin.

The family investigation did not reveal a similar case among ancestors. The diagnosis of Tietz syndrome was based on clinical criteria and pedigree. The older cousin underwent a total optical correction and a right unilateral cochlear implantation followed by speech therapy with a satisfactory result after a follow-up of two years. Unfortunately, the little cousin died following a head trauma.

Conclusion:
Tietz syndrome is a rare autosomal dominant genetic disorder, characterized by generalized albinism with bilateral profound hearing loss. It results from a non-truncating mutation in the basic domain of in the MITF gene. Its management must include, in addition to hearing and ophthalmic rehabilitation, the research and treatment of cardiac malformations which may be life-threatening.

Keywords: tietz syndrome

*Speaker

P32

Waardenburg Syndrome : about 9 cases

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Abstract

Background :
Waardenburg syndrome (WS) is an autosomal dominant inherited genetic disorder, manifests as
sensorineural deafness, defects in skin, hair, and iris pigmentation, and various neural crest-derived
tissue defects, represents 2% of the congenitally deaf population.
Objectives:
The aim is to determine the epidemiological and clinical characteristics of this group of congenitally
deaf pediatric population, to improve the management of hearing loss in particular.

Methods:
9 cases were found during the examination of children suspected of congenital deafness in ENT
department of CHU Mohamed VI Marrakech, in 13 years between December 2008 and January 2022

Results:
The median age was 3.9 years, the female sex was predominant 5F/4M, no consanguineous marriage, no fetal or perinatal history was reported, 4 cases had a family history of premature
graying, 2 cases with family history of deafness and 3 cases of heterochromia iris. All patients had
clinical features compatible with WS, 3 of them had WS type 1 with canthal dystopia, 5 cases were
WS type 2, and one case of Shah Waardenburg, there were no cases with Klein's syndrome. otoscopy
was normal in all children. Auditory evoked potentials, otoacoustic emissions and audiometry were
performed, they showed congenital, bilateral and profound sensorineural hearing loss > 100

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dB in all
cases.
All the children had received a cochlear implantation, speech rehabilitation was started early with
good results.
In our context a genetic consultation was carried out for all our children without a molecular genetic
testing .
Conclusion:
WS is a relatively common genetic cause of sensorineural hearing loss. Diagnosis is made mostly by
physical examination. Molecular genetic screening of at-risk parents allows early detection of hearing
loss in newborns. Early diagnosis and improvement of hearing loss are the most important elements
for the psychological and intellectual development of children with WS.

Keywords: waardenburg, syndrome, cochlear implantation

P33

Cochlear implants in Waardenburg syndrome : a case report

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Abstract

Introduction

Waardenburg syndrome (SW) is an autosomal dominant syndrome charcterized by association on variable degrees of dystopia canthorum, enlargement of the base of the nose, pigmentation disorders and sensorineural hearing loss. Ocular involvement may reveal this genetically and clinically heterogeneous disease that represents 2% of the hearing impaired population. Patients with SW usually present severe to profound unilateral or bilateral non-progressive sensorineural hearing loss. This is considered to be the result of thinning of the stria vascularis in the cochlea caused by a lack of melanocytes. These cells produce endolymph which is necessary to create a positive endolymphatic potential in the cochlea. Wichch is necessary for the stimulation of the inner hair cells, which transmit an electrical signal to the otic nerves. The thinning of the stria vascularis eventually leads to the collapse of Reissner's membrane followed by the destruction of the organ of Corti.

The aim of this study was to assess the long-term benefits of cochlear implants on speech perception and language comprehension in a child with SW.

Methods and material

This study concerns a child with SW who has undergone cochlear implant surgery at the ENT-HNSSpecialities Hospital in Rabat, followed by outpatient auditory rehabilitation.

Results

Our patient is a child was born to a consanguineous marriage and had an uneventful perinatal period. He had an iris heterochromia, a widening of the base of the nose, a white forelock and hyperplasia of the eyebrows (synophrys). The diagnosis of profound bilateral sensorineural deafness was made at the age of 3 years and 1 month due to delayed oral language acquisition. A genetic consultation was performed, but unfortunately the genetic

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molecular study was not performed due to lack of funds.

The cochlear implant allowed the child to perceive speech and to acheive complete oral language during the three years of follow-up.

Conclusion
This study demonstrates the similarity of performance in speech perception and language comprehension over the long term between young children with cochlear implants with and without WS. This result indicates that cochlear implantation is a good rehabilitation approach for patients with WS.

Keywords: waardenburg, Cochlear implants

P34

Syndromic sensorineural hearing loss : our serie

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Abstract

Background:
Syndromic sensorineural hearing loss are one of the most common causes of deafness. Their diagnosis, facilitated by the existence of facial dysmorphism, remains however very difficult when only auditory neurosensory impairments exist. This diagnostic difficulty can be the cause of a delay in care and significant psychosocial isolation of the child.

Objective:

Discussion of the epidemiological character of sensorineural hearing loss while insisting on the interest of a multidisciplinary collaboration in the early detection and management of these pathologies.

Methods:

This is a retrospective study on 24 children followed for syndromic sensorineural hearing loss from January 2013 to June 2020.

Results:

The average age of our patients was 7 years old. They were divided into 10 boys and 14 girls. The symptoms depended on the diagnosed syndrome: Usher syndrome (4 cases), Waardenburg syndrome (5 cases), Alport syndrome (1 case), Wolfram syndrome (2 cases), Goldenhar syndrome (3 cases), Franceschetti syndrome (1 case), otomandibular syndrome (2 cases), CHARGE syndrome (1 case), Stickler syndrome (1 case), Refsum disease (1 case), Alsrom syndrome (1 case), Cogan syndrome (1 case) and KID syndrome (1 case).

Conclusion:

A close collaboration between otolaryngologists, psychomotricians and speech therapists is essential to optimize the care of these children and avoid their confinement in total silence.
Funding: None

Keywords: Syndromic, sensorineural, hearing, loss

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P35

case study in Moroccan patients with syndromic and non syndromic hereditary deafness

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Abstract

Background : Deafness is the most prevalent human sensorineural defect. It may occur as a result of external auditory canal involvement or a deficiency in the sound conduction mechanism or impairment of the cochlea, the cochlear nerve or central auditory perception. The genetic causes are the most common, as approximately 70% of hearing disorders are of hereditary origin. A third of hereditary deafness is syndromic (associated with other symptoms) and the two thirds are non-syndromic (isolated deafness). At this date, 173 loci of deafness gene have been reported in the literature (69 DFNA, 94 DFNB, 6 X-linked DFN, 2 DFNM, 1 DFNY and 1 AUNA1). For syndromic deafness, approximately 400 syndromes associated with hearing disorders are already described. Thus, the determination of causal mutations is a valuable aid for accurate and early diagnosis. This makes it possible to better guide the management since forms of deafness respond better to the cochlear implant than others. The correct diagnosis also gives an idea of the evolutionary profile of deafness.

Methods: A whole exome sequencing was performed to identify the genetic cause of hearing loss in Moroccan families and Sanger sequencing was used to validate mutations in these genes.

The results: The results of WES revealed five variants in the genes GJB2, COL4A3, ATP6V1B1, EDNRB and MPZL2 responsible for non-syndromic and syndromic hearing loss. Multiple Bioinformatics programs and molecular modelling predicted the pathogenic effect of these mutations.

Conclusion: We identified in Moroccan deaf patients five homozygous mutations. These results show the importance of whole exome sequencing to identify pathogenic mutations in heterogeneous disorders with multiple genes responsible.

Keywords: Whole exome sequencing · Mutation · Hearing loss · Moroccan patients

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P36

sudden sensorineural hearing loss : our experience

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Abstract

Introduction :
Sudden hearing loss., is an otologic emergency and requires prompt evaluation

Background:

The SSNHL is a medical emergency requiring rapid management It poses a problem of etiopathogenesis and therapeutic protocol

Objective:

report our experience in the management of sudden deafness by focusing on our therapeutic protocol

Methods and materiel :

Between January 2012 and January 2023 a retrospective study was conducted on 32 cases with a diagnosis of idiopathique sudden sensorineural hearing loss (ISSHL). The patients were hospitalized.only cases with unilateral deafness were included. Our patients received corticosteroid therapy according to the Stennert protocol. the audiometric control was carried out in the seventh day after corticotherapy

Results:

The average age of our patients was 40 years . The average time for consultation was seven days. Influenza-like illness was found in six cases. Deafness was associated with tinnitus in 07 cases and vertigo in 2 cases. Otoscopy was normal in all our patients. A deficient peripheral vestibular syndrome was found in one case. The audiogram showed a deafness of less than 70 dB in 20 cases, a loss between 70 and 90 dB in 10 cases and a total deafness s in two cases. The videonystagmogram made in 13 cases showed, vestibular areflexia in two cases. MRI was performed in 27 cases, it was normal in 25 cases; showed a homolateral vasculo-nervous conflict in one case and homolateral acoustic neurinoma in one case.

The audiometric control showed almost complete recovery in 5 patients (14.28%), partial recovery in 15 patients (57.14%), and aggravation with total deafness in 01 case (4.76%). For the other cases the hearing remained stable

Conclusion :

The etiology of ISSNHL is still unknown. Corticosteroids are the only treatment with proven clinical efficacy at present.

Founding : None

Keywords: sudden hearing loss

*Speaker

P37

ANTIPHOSPHOLID SYNDROM WITH SUDDEN HEARING LOSS:A VERY SELDOM INDICATION OF COCHLEAR IMPLANT

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Abstract

Introduction: **Sudden sensorineural hearing loss is defined by a 30Db loss in 3 consecutive audiometric frequencies occurring under 72 hours. It is a diagnos-tic and therapeutic emergency, its positive diagnosis is obvious but its multiple etiological diagnoses should not delay auditory rehabilitation.**
The aim of our article is to draw the attention to a very rare indication of cochlear implants: profound sudden hearing loss in adults.

Methods: **We report the case of a 51 year old woman with no significant his-tory that presented with abrupt bilateral hearing loss as well as tinnitus and vertigo. Physical examination didn't reveal any abnormalities. Pure tone au-diometry revealed profound bilateral sensorineural hearing loss confirmed by brain stem auditory evoked response. Brain magnetic resonance imaging (MRI) was normal, routine blood work and auto immune screen showed the presence of antiphospholipid antibodies confirming an antiphospholipid syndrome (APS).**

Results: **Patient received multidisciplinary management including oto-rhino-laryngologists, biologists, radiologists as well as internal medicine specialists. A treatment and follow up of the APS was debuted with internal medicine specialists. In our department, patient benefited from a first-line hearing aid, with no functional improvement, and then a cochlear implant.**
Conclusion: **We observe throughout literature and our case that auditory rehabili-tation by cochlear implants extends in addition to pre-lingual and post meningitis hearing losses; to very rare cases such as profound sudden sensorineural hearing loss.**

Keywords: sudden hearing loss, antiphospholipid syndrome, cochlear implant

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P38

A case of sudden deafness due to cytomegalovirus in a 13 -year -old child: About a case.

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Abstract

Introduction:
Sudden sensory neural hearing loss (SHL) is defined as an acute unilateral or bilateral sensory neural hearing loss, with a minimum audiometric loss of 30 dB in 3 consecutive frequencies in tonal audiometry, emerging in the last 72 hours without known cause.

It is rare in children.The age of the child is a considerable factor in the choice of diagnostic and therapeutic methods. Cytomegalovirus (CMV) is among the infectious agents likely responsible.

Clinical observation:

We report the case of a 13 -year -old boy without any particular history, having consulted for a deafness of a right unilateral sudden sensory neural hearing loss. Without systemic symptoms of infection. The audiometric test has found a sensorineural hearing loss, with an audiometric loss of 50 dB in 3 frequencies , the CMV serology test was positive, the rest of the explorations being normal.

The patient underwent a course of corticosteroids , a neuroprotective treatment, as well as an anti-viral treatment.

After three days of treatment, the patient started presenting gradual clinical and audiometric improvement.

Conclusion

Sudden sensory neural hearing loss (SHL) is a rare disease, whose etiologies are diverse. Diagnosis implies an interdisciplinary process, and drug treatment does not always give good results.
This is a case in a child who has benefited from early diagnosis and management, which results in a favorable evolution.

Keywords: sudden deafness, child, Cytomegalovirus

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SUDDEN SENSORINEURAL HEARING LOSS REVEALING A LYME DISEASE

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Abstract

BACKGROUND: Lyme disease in an uncommon tick induced multisystemic infection caused by Borrelia Burgdorferi. Sudden hearing loss is a rare manifestation of this disease, especially when isolated.
OBJECTIVES: In this report, a very unusual presentation of this condition is described, in which bilateral sudden onset sensorineural hearing loss was the only manifestation. It is a rare presentation of a rare disease in Morocco. To our knowledge, it is the first case of Lyme neuroborreliosis in North Africa, with as the sole presentation: a bilateral sudden sensorineural hearing loss

METHODS: case report

RESULTS: In this paper, we describe the case of a 23 years old female patient, who presented with a two-month history of temporal headache, tinnitus and vertigo, followed by a bilateral sudden hearing. ENT examination revealed no abnormalities. Pure tone audiometry showed a complete perceptive hearing loss with thresholds of more than 100 decibels for the left ear. The MRI showed an intrasellar arachnoïdocele. The diagnosis of Lyme neuroborreliosis was made by serological testing and antibodies titration in CSF.

CONCLUSION: To gain more knowledge about the etiological role of Borrelia burgdorferi in patients with hearing and vestibular symptoms; it is, despite this rare finding, motivated to

perform Borrelia testing in patients from regions of high prevalence of tick-borne

diseases.
FUNDING: none

Keywords: lyme disease, sudden hearing loss

*Speaker

P40

Sudden hearing loss: a retrospective study about 36 cases

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Abstract

The aim of this study is to describe our experience on the management of sudden hearing loss by highlighting the notion of urgency and by showing the factors affecting the probability of recovery. We report a retrospective study including 36 patients treated in the Department of Otolaryngology – Head and Neck Surgery at the Avicenne Military Hospital in Marrakech, Morocco, between January 2010 and December 2015. Only unilateral sudden hearing loss was included in our study (21 right ears and 15 left ears). The clinical data were collected by the interview and the full clinical examination. Hearing impairment was evaluated at admission, every 48 hours and after treatment with pure-tone audiometry. All our patients underwent auditory brainstem response (ABR), 09 of them a computed tomography. MRI was performed in a single case. The therapeutic protocol included corticosteroids and vasodilators. Only 16.6% of patients recovered the entire initial hearing loss. The auditory brainstem response (ABR) detected a case of acoustic neuroma confirmed by imaging.

Keywords: sudden, hearing loss, inner ear

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P41

MENIERE'S DISEASE

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Abstract

Introduction:

Menièr's disease is an inner ear disorder of uncertain pathogenesis which typically manifests with episodes of vertigo associated with cochlear symptoms: hearing loss, tinnitus and aural fullness. It has 0.2% prevalence and well defined clinical criteria.

Objective:

The aim of our study is to describe the clinical profile and management difficulties of patients affected by menière's disease in our department.

Patients and Methods:

A retrospective observational patient study was conducted in the ENT Department of Ibn sina University Hospital in Rabat, including the follow up of 4 patients with menière's disease during the year 2022.

Résultats

- 100% of patients had no prior medical history linked to the disease at study;
- 75 % of patients presented with the full triad : Vertigo-tinnitus-healing loss;
- Vertigo episodes were the most frequent clinical presentation (100%);
- All patients had normal otologic examination ;
- Vestibular examination was normal in 75% of patients, with no vertigo episodes "attacks", a spontaneous nystagmus was revealed in 1 patient examined in an acute setting.
- Neurologic examination was normal in all patients;
- Pure tone audiometry was conducted for all patients. Revealed low frequency unilateral sensorineural hearing loss in the affected ear in 25% of patients and a mixed hearing loss (conductive and sensorineural) in 75% of patients;

*Speaker

- Tympanometry revealed normal tympanic membrane compliance in all patients.
- Videonystagmography was conducted in all patients and revealed vestibular hyporeflexia of affected ear in only 50% of patients ;
- MRI showed normal findings in 75% of patients and revealed significant endomymphatic hydrops in 25% of them (grade III) ;
- 75% of patients were treated with acetyl-leucine for management of acute vertigineous episodes and betahistine as a first line treatment. One patient was treated with intra tymanic steroid injections and placement of T-tubes bilaterally after resistance to first line treatment.
- Long term evolution observed in all patients: Positive outcome in the patient that received steroid injections and placement of T-tubes, negative outcome in the rest of patients that received first line treatment (which continue experiencing intense vertigo episodes).

Keywords: meniere's, videonystagmography, management

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Meniere's disease : results of videonystagmography

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Abstract

Background : Ménière's disease is an inner ear condition of unknown aetiology characterized by rotational dizziness, fluctuating hearing loss, tinnitus, and aural fullness sensation. The prevalence is 0.2% and the diagnosis is clinical based on well-defined criteria.
Objectives: To study through a series of cases the interest of VNG in the diagnosis of Menière's disease.

Methods: This is a retrospective descriptive study of patients followed at the Mohammed 6 University Hospital in Marrakech for meniere's disease who underwent VNG over a period of 6 years from January 2016 to January 2022 .

Results: We selected 52 patients with a mean age of 49.7 years and extremes of 25 to 79 years. There were 35 women and 17 men. The majority of our patients had as clinical symptoms: recurrent vertigo attacks, hypoacusis and tinnitus. Vestibular exploration by VNG was normal in 9 patients and objectified a unilateral vestibular hyporeflexia in 67.5% of the patients (n=22) while 6 patients presented a hyporeflexia in the contralateral normal ear.

Conclusion : Our findings revealed that VNG is a suitable tool for vestibular function assessment in Meniere's patients and among its subcomponents, caloric irrigation constitute the most sensitive test.
Funding : none

Keywords: Meniere disease, videonystagmography, vestibular hyporeflexia

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Etio-pathogeny of Meniere's disease A multicentric study

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Abstract

Introduction:

Meniere's disease is a chronic affection of the inner ear. Though its cause is still unknown, the pathological substratum is an endolymphatic hydrops.

This disease presents as the association of fluctuating deafness, vertigo with remarkable neuro-vegetative symptoms, and tinnitus. It appears from the third to the seventh decade of life, with a slight female predominance. The fact that it has higher prevalence in Caucasians, and is very rare among sub -Saharan Africans suggests a genetic contribution. It can be associated with several comorbidities such as arthritis, psoriasis, gastroesophageal reflux, irritable colon syndrome and migraine.

Objective:

This work aims to study the various factors and mechanisms incriminated in the occurrence of Ménière's disease.

Material and methods:

This is a multicenteric study based on studies carried out in 18 European, 4 American and 2 Asian centers.

Result:

Multiple factors contribute to the developement of Meniere's disease. Extrinsic causes are: Infections, chronic average otitis, inflammation, otospongiosis, trauma, allergies, or auto-Immune diseases.

On the other hand, genetic and immunological factors seem to play a central role in Ménière's disease. The genetic etiology explains the disease's history, evolution and clinical signs, the bilateral and familial forms, as well as predisposition factors.

Although Ménière's disease is generally sporadic, it is a dominant autosomic transmission is

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observed in about 5 % of cases, mitochondrial recessive forms have also been reported. No clinical difference was found between sporadic and family cases in the various works, with the exception of an early start in familial cases.

Other studies suggest that more than a third of cases of Ménière's disease have an autoimmune origin.

Conclusion:
Understanding the etiopathogeny of Meniere's disease has been the subject of different research studies in the last decades, several hypotheses were suggested in order to clarify the etiologiy of this disease; Which will be useful in improving diagnostic tools, as well as establishing targeted and personalized therapies.

Keywords: Meniere's disease, pathogeny, inner ear

P44

Audiogram and clinical patterns of meniere disease

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Abstract

We conducted a retrospective study in a group of patients with diagnosed meniere disease. The aim of this study is to investigate the symptom patterns as well as the audiological profil of this disease. Medical records and pure-tone audiograms of 29 patients were analyzed. We also studied the age of onset, sex ratio and incidence of bilaterality. The age of onset was 44 years old and the female to male ratio was 4.8. The incidence of bilaterality was 27.5%. The most common symptoms were vertigo and tinnitus followed by hearing loss and aural pressure . The most common audiogram was the peak-type by far, next the falling-type , and then the flat-type. We suggest, the peak type audiogram is very indicative of the presence of a meniere disease.

Keywords: meniere disease audiogram vertigo tinnitus

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P45

Release Rates of Prednisolone-21-Hydrogen-Succinate from 3D-Printed Silicone as Material for Patient-Individualized Drug Releasing Implants

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Abstract

Introduction: For the treatment of sudden sensorineural hearing loss or *Morbus Meniére* prednisolone-21-hydrogen-succinate (prednisolone) is routinely used. A long term local application of the drug via an implant is preferable to a systemic treatment or intratympanic injection, as an implant can achieve a sustained therapy with a biologically relevant dosage. In order to optimize the result, such a drug-eluting implant can be of a patient-specific shape and size. We developed a workflow to additively manufacture such implants and evaluated the prednisolone loading capacity and release kinetics.
Methods: To investigate the release rates of prednisolone from 3D-printed silicone samples, three different geometries with four different prednisolone concentrations each (1, 5, 10 and 20% (w/w)) were manufactured and incubated in artificial perilymph for 56 days. The supernatant was collected at various time points and analyzed via Ultra High Precision Liquid Chromatography.

Results: Prednisolone can be incorporated into silicone and the composition is 3D-printable. After a burst release within the first hour, the release rates decreased permanently in the following 10 days with subsequent near-constant release rate until day 56. Both, geometry and hardness of the samples affected the release rate. A higher surface-to-volume-ratio resulted in an up to four times higher release. A softer sample, as a result of an higher drug concentration of 20%, had a 16-times higher release rate compared to the 10% samples, even though the concentration was only twice as high.

Based on the geometries and hardness between 3 and 36% of the total added drug content was released within the first 56 days.

Conclusion: Prednisolone and silicone can be 3D-printed in different surface-to-volume-ratio. The geometry as well as the hardness affect the release rates. The drug-material combination can be used in future develop of 3D-printed, drug releasing, patient-individualized implants to locally treat inner ear pathologies by pharmacotherapy.
This work was funded by HighTec Inkubator SMINT@Hannover.

Keywords: release kinetics, release rates, prednisolone, silicone, drug delivery, 3d printing, implants, patient individualized, drug release

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P46

Effects of Molecular Nano-Motor (MNM) -NOX3-dsiRNA-delivered by intracochlear infusion in a cisplatin-induced hearing loss model in Hartley Guinea pigs

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Abstract

INTRODUCTION

Knockdown by local administration of NOX3-siRNA prevents cisplatin ototoxicity. However, due to their size and negative charge, the diffusion of the siRNAs into the cells is limited. Aposense's innovative and unique technology is comprised of novel Molecular Nano-Motors (MNMs), small molecules which are conjugated to dsiRNA and interact with the electric field inherent to all cell membranes to achieve transmembrane delivery of their nucleic acid cargo. Our study aims to demonstrate the innovative potential of using MNM-dsiRNA in hearing disorder therapies. Using intracochlear (IC) infusion, we studied (1) a comparative biodistribution profile between Cy3-dsiRNA and MNM-Cy3-dsiRNA in the cochlea; (2) the protective effects of dsiRNA and MNM-dsiRNA against NOX3 on cisplatin induced hearing loss (CIHL).

METHODS

In the biodistribution experiment, Cy3-dsiRNA and MNM-Cy3-dsiRNA were intracochlearly infused for 24 hours in male Hartley Guinea pigs. The dsiRNA compounds were intracochlearly delivered using an Alzet osmotic pump. Six hours after infusion, cochleae were sampled for flat surface or cross section preparations. The biodistribution of Cy3-dsiRNA and MNM-Cy3-dsiRNA was observed at the apex, mid and base of the cochlea, and targeted cells identified in comparison to naïve cochleae.

For CIHL in male Hartley Guinea pigs, for 24 hours, an iPRECIO pump intracochlearly delivered vehicle, dsiRNANOX3 and MNM-dsiRNANOX3. Infusion started 24 hours before slow IP administration of cisplatin (10 mg/kg). ABR and DPOAE were measured prior to pump implantation and 3 days after cisplatin infusion (T+3DAYS).

RESULTS AND CONCLUSIONS

In the biodistribution study, both flat surface and cross section preparations demonstrated greater biodistribution of MNM-Cy3-dsiRNA from base to apex and a better penetration in all cochlear cell types than Cy3-dsiRNA.

At T+3DAYS, the CIHL demonstrated by lower DPOAE amplitudes and greater ABR thresholds was significantly prevented by MNM-dsiRNANOX3. No effect was observed after dsiRNANOX3 treatment.

Keywords: hearing loss; cisplatin; NOX3; dsiRNA; MNMs; ABR; DPOAE; intracochlear infusion.

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P47

The Clinical Effect of Steroids for Hearing Preservation in Cochlear Implantation: Conclusions Based on Three Cochlear Implant Systems and Two Administration Regimes

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Abstract

The main aim of this study was to assess the clinical effect of steroids (dexamethasone and prednisone) on hearing preservation in patients who underwent cochlear implantation with different cochlear implant systems (Oticon®, Advanced Bionics®, Med-El®). 147 adult patients met the inclusion criteria and were enrolled to the study and divided into three groups depending on the brand of cochlear implant they received and participated in all follow-up visits regularly. They were also randomly divided into three subgroups depending on the steroid administration regime:
(1) intravenous dexamethasone (0.1 mg/kg body weight twice a day for three days); (2) combined intravenous and oral steroids (dexamethasone 0.1 mg/kg body weight twice a day plus prednisone 1 mg/kg weight once a day); and (3) no steroids (control group). The results were measured by pure tone audiometry (PTA) at three-time points: (i) before implantation, (ii) at processor activation, and (iii) 12 months after activation. A hearing preservation (HP) figure was also calculated by comparing the preoperative results and the results after 12 months. Further measures collected were electrode impedance and hearing threshold in the non-operated ear. The highest HP measures
(partial and complete) were obtained in the subgroups who were given steroids. Of the 102 patients given steroids, HP was partial or complete in 63 of them (62%). In comparison, partial or complete HP was achieved in only 15 patients out of 45 (33%) who were not given steroids. There were differences between the three cochlear implant groups, with the Med-El and Advanced Bionics groups performing better than the Oticon group (45% and 43% of the former two groups achieved partial or complete HP compared to 20% in the latter). Hearing thresholds in the non-operated ear were stable over 12 months. Generally, impedance was slightly lower in the 12-month follow-up in comparison with the activation period, with the exception of the Oticon group. (4) Conclusions:
Pharmacological treatment with steroids in patients undergoing cochlear implantation helps to
preserve residual hearing.

Keywords: cochlear implantation, steroid administration, partial deafness treatment, dexamethasone, prednisone

*Speaker

P48

Immune checkpoint inhibitor therapy did not influence hearing ability in the most sensitive frequency range, but mitigated outer hair cell loss in the basal cochlear region in C57BL/6J mice

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Abstract

The administration of immune checkpoint inhibitors (ICIs) often leads to immune-related adverse events. However, their effect on auditory function is largely unexplored. Thorough preclinical studies have not been published yet, only sporadic cases and pharmacovigilance reports suggest their significance. Here we investigated the effect of anti-PD-1 antibody treatment (4 weeks, intraperitoneally, 200 μg/mouse, 3 times/week) on hearing function and cochlear morphology in C57BL/6J mice. ICI treatment did not influence the hearing thresholds in click or tone burst stimuli at 4-32 kHz frequencies measured by auditory brainstem response. Number and morphology of spiral ganglion neurons were unaltered in all cochlear turns. The apical-middle turns ($<$ 32 kHz) showed preservation of the inner and outer hair cells (OHCs), whilst ICI treatment mitigated the age-related loss of OHCs in the basal turn ($>$ 32 kHz). The number of Iba1-positive macrophages has also increased moderately in this high frequency region. We conclude that a 4-week long ICI treatment does not affect functional and morphological integrity of the inner ear in the most relevant hearing range (4-32 kHz; apical-middle turns), but a noticeable preservation of OHCs and an increase in macrophage activity appeared in the $>$ 32 kHz basal part of the cochlea. *Funding*: Hungarian Scientific Research Fund (NKFIH K-128875); "Higher Education Institutional Excellence Programme", framework of the Therapeutic and Neurology Development thematic program of the Semmelweis University (TKP-EGA-23); European Union's Horizon 2020 research and innovation programme (No 739593).

Keywords: immune checkpoint inhibitor, anti, PD, 1 therapy, ABR, cochleogram, hair cells, macrophages

*Speaker

P49

Intra-tympanic injections to treat miniére disease

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Abstract

Intra-tympanic injections of corticosteroids and gentamycin are recommended as a secondary treatment for miniére disease after failure of medical treatment.
In this presentation, we will discuss the indications and the contraindications of this treatment and we will explain the techniques used, on the basis of a review of the literature.
In conclusion, we will see if the literature can provide a consensus on the use of intra-tympanic aminoglycoside treatment.

Keywords: Intra, tympanic injections, corticosteroids, aminoglycoside

*Speaker

P50

MANAGEMENT OF SENSORINEURAL DEAFNESS SECONDARY TO TEMPORAL BONE TRAUMA: A REPORT OF 23 CASES

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Abstract

Background:
Temporal bone fractures often lead to loss of audio-vestibular function. Otic capsule violating fractures are associated with higher incidence of Sensorineural hearing loss than otic capsule sparing fractures.

Objectives:

Our study aims to investigate the management of sensorineural deafness in temporal bone trauma

Material and methods:

Prospective study conducted at the Mohammed VI University Hospital center of Marrakech, from January 2017 to June 2022, covering 23 cases of sensorineural hearing loss in the context of Temporal bone trauma.

Results:

The mean age was 31 years (4-56 years), with a clear male predominance (sex ratio 21/2). Clinical symptomatology was characterized by hearing loss in all our patients, otorrhagia in 20 cases, vertigo in 13 cases, facial paralysis in 10 cases, and otoliquorrhea in 5 cases. 96% of patients (22 patients) presented with labyrinthine fractures. Two cases of pneumolabyrinth and three cases of bilateral temporal bone fracture were noted. The audiometry showed sensorineural hearing loss in 9 cases and mixed in 14 cases. The hearing loss was mild in 52% (between 21db and 40db) of cases, moderate (between 41db and 70db) in 31%, and sever (between 71db and 90db) in 17% cases. In three cases, the hearing loss was bilateral with severing sensorineural hearing on bilateral. Treatment was most often conservative by

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corticosteroids: 1mg/kg of prednisone, prophylactic antibiotics. The clinical course after one month of the trauma was marked by the spontaneous improvement of the mixed deafness in 6 cases. The persistence of sensorineural deafness in the other cases with evolution towards total hearing loss in 7 cases. For the three patients with bilateral fracture, they have benefited from a cochlear implantation.

Conclusion:

Temporal bone fracture is one of the most common traumatic injuries that can cause loss of auditory and vestibular function. The diagnosis must be made within a few hours after the trauma, as the auditory prognosis depends on the earliness of the management. Auditory sequelae can go as far as complete hearing loss, on the affected side.
Funding : None

Keywords: Hearing loss, Tonal audiometry, Temporal bone, Otoscopy, Otorrhagia, Ear drum, Cerebrospinal fluid leak, Rhinoliquorrhea, Hemotympan, Facial paralysis, Pneumolabyrinth, Prophylactic antibiotics, Prednisone, Auditory nerves, Brain

P51

Psychological and therapeutic aspects of chronic tinnitus

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Abstract

Background

Tinnitus is defined as a subjective acoustic perception in the absence of any external source, its prevalence is estimated to 10-16% for chronic tinnitus in the adult population; and increases with age.

Objectives

The objectives of our study are to assess the different psychological and therapeutic aspects of chronic tinnitus, including psychological impact on patients, pharmacological therapy and the types of psychological interventions.

Methods:

A bibliographic review based on Medline and Scopus database research

Results:

While the majority of the population is unaffected by tinnitus, 0.5-3% of the adult population experience distress and impairment in everyday life. Moreover, distressing tinnitus is often associated with psychological problems such as anxiety and depressive symptoms.

Most widely used treatments for tinnitus involve counselling, and best evidence is available for cognitive behavioural therapy. New pathophysiological insights have prompted the development of innovative brain-based treatment approaches to directly target the neuronal correlates of tinnitus. The use of pharmacotherapy is not well supported by prospective, randomized, placebo-controlled clinical trials. Various drugs have been shown to be effective in some studies, but the clinical evidence is limited. Cognitive behavioural therapy is the most common intervention conducted by the researchers. The length of therapy ranges from six weeks to three months. Psychological interventions are more effective in reducing psychological impacts of tinnitus than non-psychological interventions such as the use of tinnitus maskers. Nevertheless, the combination of the treatments gives superior outcomes.

Conclusions.

A large variety of therapeutic interventions is already available, which can efficiently reduce tinnitus severity. Several innovative treatment approaches are currently under development. Simplified version of psychological intervention that can be implemented by other clinical professionals should be developed to treat tinnitus.

Keywords: Tinnitus, Therapeutics, Psychology

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P52

Intralabyrinthine Hemorrhage After General Anesthesia: Case Report

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Abstract

Introduction :
Intralabyrinthine haemorrhage is a rare cause of acute idiopathic unilateral cochleovestibular deficit. Several etiologies have been identified such us anticoagulant treatments and blood diseases.

Objective :

Through this presentation, we report a case of intralabyrinthine hemorrhage secondary to a brief general anesthesia.

Case Presentation :

A 58-year-old woman was referred by gastroenterology department for sudden deafness associated with vertigo in the immediate aftermath of a colonoscopy under general anesthesia. She has a twenty-year history of neuro-syphili, and colonic adenocarcinoma treated with surgery and adjuvant chemotherapy in 2004.

noted normal tympanum. Tone audiometry performed the same day revealed a left cophosis and a right sensorineural hearing loss of 60 dB. Auditory Steady-State Responses (ASSR) performed on the tenth day confirmed the left cophosis.

Magnetic resonance imaging was in favor of an intralabyrinthine hemorrhage

The clinical course was marked by progressive regression of vertigo in 15 days. The cophosis was persistent three months after the first ENT consultation.

Discussion

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Intralabyrinthine hemorrhage is a rare cause of acute cochleovestibular deficit. Several causes have been identified, including anticoagulant treatment and hematological diseases.

The intervention sheet does not mention any blood pressure lability (blood pressure oscillating between 90/60 mmHg and 120/75 mmHg).

Our patient had undergone colonoscopy under general anesthesia with Propofol. Propofol is known as a drug that causes controlled arterial hypotension and vasodilatation of the surgical site.

However, despite this vasodilatory and hypotensive effect, Propofol can cause capillary bleeding despite a low systolic pressure.

The evolution of intralabyrinthine hemorrhage is unfortunately not very favourable with persistent deafness in most cases.

Conclusion :
Intralabyrinthine hemorrhage should be evoked in front of any acute cochleo-vestibular syndrome in a vascular terrain or coagulation disorders. No previous case of intra labyrinthine hemorrhage secondary to general anesthesia have been reported in the literature.

Keywords: Intralabyrinthine Hemorrhage, General Anesthesia, Deep Deafness, Vertigo, MRI

P53

Screening for cochleovestibular disorders in neurologic diseases

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Abstract

BACKGROUND:
Cochleovestibular disorders are a commun pathological entity in certain neurological diseases involving cochlear and/or vestibular nerves. These diseases include multiple sclerosis (MS), Fabry disease, neurosyphilis, neurobehcet's disease, neurosarcoidosis... These disorders may be indicative of the disease or occur during its course.

OBJECTIVES: The aim of this study was to detect these cochleovestibular disorders in patients with neurological diseases.

METHODS:

This is a prospective study of 30 patients with neurological diseases who were screened for cochleovestibular disorders. The audiometric evaluation consisted of pure-tone audiometry, otoacoustic emissions (OAE), videonystagmography and caloric tests.

RESULTS:

Our study had included 15 patients with MS under treatment, 7 cases of neurobehçet, 3 of neurosarcoidosis, 4 of neurosyphilis and a case of Fabry disease. 53.33% of our patients had unilateral hearing loss, 30% had rotatory vertigo while 30% were asymptomatic. Pure-tone audiometry showed a mild sensorineural hearing loss in 36.6%, severe in 6.66% and normal in 26.6% of patients. OAE were negative in 30% of cases. auditory evoked potentials showed a prolongation of the latency of the wave V in 10% of the cases. The eye-tracking test was abnormal in 26.6%. The ocular saccades test was abnormal in 50% of cases with a pathological refixation latency in 34%. The optokinetic reflex was negative with a low gain in 43.33% of the cases. The Head Shacking Test was positive in 11 of our patients. The caloric tests showed right hyporeflexia in 11 cases, left hyporeflexia in 6 cases and right areflexia in 2 cases. 17 of our patients had an improvement of their symptoms after therapeutic adjustment.

CONCLUSION:
Some neurological diseases may be associated during their evolution with cochleovestibular manifestations that can sometimes be irreversible. Hence the interest in early screening and a quick and well-managed treatment.
FUNDING: None

Keywords: screening, Hearing loss, vertigo, neurological diseases

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Audiovestibular disorders screening in systemic autoimmune diseases

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Abstract

Background : audiovestibular disorders can occur during many multisystem autoimmune, vascular or inflammatory diseases. It is important to know the spectrum of these multisystem diseases, these disorders can be revealing. or they can also occur during these chronic deseases
Objectives: Detecting cochleovestibular disorders in patients with systemic diseases

Methods : Prospective study including patients followed for systemic disease within the CHU mohamed VI of Marrakech in a period of one year from January 2022 until December 2022, 30 patients were collected

Results : The average age was 45 years (28-57), sex ratio = 2 / 1, no patient revealed particular otological history,

The patients were followed for: Behcet's disease (7 cases), systemic lupus erythematosus (5 cases), sarcoidosis (4 cases), Wegner's disease (4 cases), goujerot sjogren's syndrome (3 cases), rheumatoid arthritis (2 cases).), cogan syndrome (2 cases), Vogt-Koyanagi-Harada disease (2 cases), giant cell arteritis (1 case)

The main symptoms were represented by hearing loss in 23 patients (78% of cases), tinnitus (60% of cases), and vertigo in 10 patients

the audiometric result showed mild sensorineural hearing loss in 12 patients, moderate in 7 patients and severe in 1 patient,

Vestibular examination found abnormal vestibular function in 80% of cases with 20% of cases presenting with spontaneous or gaze-induced nystagmus, 14 patients had reduced caloric response, 4 patients had no caloric response.

All patients were put on long-term corticosteroid therapy , 20% of cases were reassessed and showed clinical and audiometric improvement

Conclusion : Cochleovesibular disorders may be found during various multisystemic diseases, they play a role in the diagnostic process of autoimmune diseases, which is essential to increase the chances of restoration when a specific treatment is quickly initiated
Funding : NONE

Keywords: Audiovestibular, autoimmune diseases, systemic diseases

*Speaker

P55

BENINGN PAROXYSMAL POSITIONAL VERTIGO : 40 CASES

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Abstract

Introduction :
Benign paroxysmal positional vertigo is an intense vertigo that occurs during particular head movements, in particular conditions for a single patient, with no associated cochlear symptoms. The diagnosis is clinical and treatment widely relies on vestibular rehabilitation.

Objective :

Study the epidemiological, diagnostic, therapeutic and evolutionary aspects of patients seeking medical attention for BPPV at the ENT department of specialties hospital in Rabat.

Methods:

A retrospective and observational study about 40 patients seeking medical attention for BPPV from January 2019 to January 2020 at the ENT department.

Results:

- 21% of patients seeking medical attention for dizziness had a BPPV.
- Sex ratio is 0,6.
- Age mean is 52 years.
- 10% had medical history of high blood pressure, 20% had headaches, 7,5% had head trauma,5% had vestibular neuritis, 2,5% had Meniere's disease.
- Most associated symptoms were tinnitus in 42,5% of patients and hearing loss in 22,5% of cases.
- Vestibular examination was normal 82% of cases, in the rest of patients vestibular examination was deemed difficult.
- A positive Dix & Hallpike maneuver in 95% of patients.
- All patients benefited from tone audiometry, normal in 9 patients, Videonystagmography conducted in 5 patients.
- 3 patients had prior cerebral CTs done, cerebral MRI was done for 2 patients.

*Speaker

- The liberatory maneuvers that were conducted: Semont in 55% of cases and Epley for 44% of patients.
- Vertigo was recurrent in 38% of patients with Semont maneuver and in 61% of patients with Epley maneuver.

Conclusion:BPPV is the most common cause of peripheral vertigo and should thus be searched for in all patients presenting with vertigo.It is defined clinically and its diagnosis calls for a detailed medical history and meticulous physical examination. BPPV should be thought of after careful exclusion of the differential diagnoses especially tumors. Treatment is based on vestibular rehabilitation.

Keywords: BPPV, liberatory maneuvers, Videonystagmography

P56

Ocular Motor Impairment in Early-Stage Multiple Sclerosis: A Video-Oculography Assessment.

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Abstract

Background: Eye movement disorders in multiple sclerosis (MS) are frequently misdiagnosed and frequently overlooked during clinical examinations. Even at a preclinical state, these defects frequently cause impairment and weariness.
Objectives: By using VNG registration, we aim to specify the frequency of nystagmus, eye movement impairments and vestibular reflexes abnormalities in our MS patients.

Methods: We conducted a cross-sectional observational study including 20 individuals with a confirmed MS diagnosis. The inclusion criteria were an EDSS score of 4 or less and a 6-month interval between the last relapse and enrolment.

As part of the MS assessment, a routine ORL, neurology exam, eye exam, assessment of eye movement using Ulmer's videonystagmography battery tests, and routine brain MRI were performed on the patient.

Results: A total of 75% of the patients in our series are female, with a mean age of 39 years and a range of 24 to 59 years. The average age of MS onset is 32 years. The relapsing-remitting type of multiple sclerosis (RRMS) accounts for 95% of all cases. Principal VNG manifestations are related to subclinical eye movements abnormalities. Rotatory vertigo caused by vestibular dysfunction was less prevalent than other balance disorders. There were found to be two types of nystagmus: pendular and central positional nystagmus.
Conclusions: VNG is sensitive for detecting vestibular system dysfunction in MS patients. It is also beneficial for diagnosing subtle eye movement abnormalities that are usually overlooked.

Keywords: Multiple sclerosis, Videonystagmography, Eye movement abnormality, Nystagmus, Vestibular syndrome

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P57

CLASSIFICATIONS OF VESTIBULAR MALFORMATIONS

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Abstract

Introduction: Inner ear malformations account for 20% of hearing loss in children. They can affect the cochlea, the vestibule but also the other elements of the inner ear. Isolated vestibular malformations are very rare and heterogeneous.
Objectives: This work aims to study and describe published classifications of vestibular malformations, and to cite the role of each in prognosis and management

Materials and method: Multicenteric study of 12 international centers from 1791 until 2022.
Results :

More than two hundred years ago, Carlo Mondini described the first malformation of the inner ear. From then on, many classifications were used: Omerod and Schuknecht (1960), Valvassori (1969), Jackler (1987), Phelps (1992), Marango (1997), then Zheng (2002), and Sennaroglu. (2002).

We have found that the most widely used and globally recognized classification, which is that of Sennaroglu in 2002, modified in 2010 and 2017: It is based on the Jackler classification and contains 8 categories.

Afterwards, in 2019, SMS (Sawai Man Singh) from India proposed a new, simpler classification containing 4 categories. Then Kenna D. Peusner et all. (2021) described vestibular malformations from a genetic pathophysiological point of view.

Discussion :

The classifications described are based on the stage of interruption of the inner ear's embryonic development, an do not account for all types of vestibular malformations. Hence the need for a uniform, simple and standardized classification that could simplify management for clinicians.

Conclusion:

Until now, there is no classification specific to isolated vestibular malformations. All those published contain both vestibular malformations and cochlear malformations. The development of new technologies, particularly in radiology and genomic studies will have a considerable impact on these classification systems.

Keywords: malformation, cochleovestibular, classification.

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P58

Vascular loops in the AICA and vestibular dysfunction ; about two cases

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Abstract

Introduction :
Neurovascular conflicts of the cerebellopontine angle are rare entities that result from the anatomical contiguity of the vascular and neural elements in this region, they are observed in the 5th, 7th, 8th and 9th cranial nerve pairs. The diagnosis is based on MRI, AEP, Pure Tone Auditory, VNG.

Case Presentation :

-Patient n○1

67 years old man with no relevant medical history , presented with a history of bilateral intractable tinnitus and progressive bilateral hearing loss of more than one year and bilateral tinnitus, one month ago he presented positional vertigo.

On examination the patient didnt present any otological , vestibular nor neurological symptoms

Explorations : Pure tone audiometry indicates a bilateral sensorineural hearing loss

: MRI of the cerebellopontine angle shows a vascular loop of the right AICA with type II vascular conflict

: VNG found vestibular areflexia on the right side

-Patient n○2 :

62 years old women with no relevant medical history, presented with a history of headaches of more than 6 years and vertigo associated with left unilateral tinnitus of almost 4 months. On examination the patient didnt present any otological , vestibular nor neurological symptoms.

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Investigations : Pure tone audiometry indicates a mild conductive unilateral hearing loss in the left ear

: MRI of the cerebellopontine angle shows a vascular loop of the left

AICA coming into contact with the acoustic-facial bundle.

: VNG found vestibular areflexia on the left side

Discussion :

When the neurovascular conflict of the cerebellopontine angle concerns the VIII cranial nerve, the usual revealing signs are positional vertigo, unilateral tinnitus and progressive unilateral sensorineural hearing loss. However, the existence of vascular loops can be a sim-ple coincidence and not pathological.

Auditory evoked potential (AEP) is used to suggest the nerve origin of the symptomatology. MRI determines the location of the conflict, the deformity of the nerve or the ACAI and its pathway in relation to the nerve pathway, and Magnetic resonance angiography (MRA) bet-ter defines the aretery involved. The treatment of symptomatic patients is based on medical treatments by voltage dependent sodium channel blockers , in case of failure of the latter, the surgical treatment consists in dissecting and releasing the artery and maintaining it at a distance from the nerve.

Conclusion :
Neurovascular conflicts of the AICA is a rare and underestimated entity, although they can be asymptomatic the clinical manifestations can be atypical and differ depending on the type of the neurovascular conflict. The diagnosis is based primarily on MRI that allows to localize and identify the nature, 87% are of vascular origin.

Keywords: AICA, vestibular dysfunction, vertigo

P59

Labyrinthine fistula on middle ear cholesteatoma: about a case

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Abstract

Introduction:

Cholesteatoma of the middle ear is a destructive lesion, with a potentially erosive character for the bone. The search for signs suggestive of complications must be systematic, labyrinthine fistula is the most frequent.

Observation:

The patient was a 16-year-old boy with a history of recurrent otitis media, hospitalized for the management of vertigo and nausea with notion of fetid otorrhea and left hypoacusis. Examination with the otoscope objectifies a non-controllable, non-self-cleaning attic retraction pocket. Examination with the otoscope objectifies a non-controllable, non-self-cleaning attic retraction pocket. C-/C+ brain scan: presence of tissue filling in the left middle ear of the left middle ear, responsible for ossicular lysis. CT scan of the rocks: appearance of a cholesteatomata's otitis with labyrinthine extension. MRI in favor of a left otitis of cholesteatomata's origin complicated by a labyrinthine fistula.

Discussion:

Labyrinthine fistula is the most common complication in chronic cholesteatomata's otitis. The most common location is the lateral semicircular canal in over 90% of cases. A vestibular manifestation is present in only 1 out of 2 cases, and the absence of a clinical sign of the fistula does not in any case allow the elimination of a labyrinthine fistula. Therefore, any cholesteatoma of the middle ear should raise the possibility of a labyrinthine fistula. Additional MRI imaging could show a disappearance of the blood-labyrinth barrier in the incriminated canal. The surgical treatment has three main objectives: the complete removal of the cholesteatoma, which is the only guarantee against the development of a residual cholesteatoma, the prevention of recurrence by an adapted technique, preferably in a single time, and the restoration of a quality hearing function.

Conclusion:

The labyrinthine involvement during cholesteatoma is essentially related to labyrinthine fistulas ranging from simple erosion of the bony shell to complete destruction with exposure of the membranous labyrinth.

Keywords: The cholesteatoma, the middle ear, Labyrinthine fistula

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P60

EPIDEMIOLOGY OF PAROXYSMAL POSITIONAL VERTIGO BENIN IN ENT CONSULTATION,Retrospective study of the H.M.A about 90 cases

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Abstract

Introduction:
Vertigo is an illusion of movement that manifests itself as a feeling of rotation or pseudo-drunkenness. It is often accompanied by neurovegetative signs. The patient remains conscious throughout the crisis.

This is a frequent reason for consultation in ENT. It varies from the simple feeling of imbalance to disabling vertigo.

PPVB is the main etiology of peripheral vertigo.

Materials and methods:

Retrospective study, carried out over a period of 3 years (01/2020-01/2023) in ENT consultation of a single doctor of the otolaryngology department of the Avicenna Military Hospital Marrakech.

The purpose of our work is to:

Assess the incidence of PPVB in relation to different parameters: sex, age, occupation, etiology, offending side, therapy used and evolution after treatment.

Analyze the results obtained and compare them with those reported by the literature

Results:

*Speaker

90 cases of dizziness were identified in our study: 50 women (60%) and 40 men (40%)

The right side is the most incriminated 58%.

Liberating maneuvers are the main treatment with a success rate of 70% after a first maneuver and which reaches 90% after a second.

Recurrence after adequate treatment is uncommon about 10% of cases

Conclusion:

Dizziness and instability are often of vestibular origin. It should be remembered that PPVB is the most frequently encountered vertigo and that it represents 40% of pathologies.

The clinical history and the first clinical signs are important to describe in order to establish the most appropriate treatment, which will often be vestibular physiotherapy. In PPVB, it is the only effective treatment.

Keywords: VERTIGO, PPVB, ENT, MILITARY HOSPITAL, MARRAKECH, LIBERATING MANEUVERS, VESTIBULAR

P61

Correlation between intraoperative neural response telemetry and behavioral levels in pediatrics cochlear implant.

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Abstract

Background :

A number of clinical trails have been carried out to study the correlation between the neural response threshold and the behavioral levels used for cochlear implant programming processes but results have not been unanimous. An important question can the NRT threshold be used to approximate T- and/or C-level remains.

Objectives: To determine the relationship between the electrically evoked nerve action potential (Neural Response Telemetry (NRT)) and behavioral levels (T- and C-level) for pediatric patients using the cochlear implant system.

Methods: A hospital based study of pediatric cochlear implant patients in the period between June 2014 and December 2020 at Mohamed IV University Hospital Marrakech. The Neural Response Telemetry was administered to 47 children (mean age at implantation: 4 years) with the cochlear implants. Four intra cochlear electrodes (numbers 5, 10, 15, and 20) were tested one-month post-implantation, the neural response threshold compared with the behavioral threshold and the maximum comfort level estimated at the same time.

Results: At all the electrode numbers, the mean for NRT level measurements was significantly higher than that for the T-level measurements and the mean for the C-level measurements was significantly higher than that for NRT level measurements The correlation analyses showed positive correlation between C-level and NRT level measurements and T-level and NRT level measurements.
Conclusion: There was a positive correlation between NRT value measurements and both T and C value measurements. Therefore, it is useful to use the NRT values to predict the behavioral T and C values in prelingual children.

Keywords: NRT, behavioral levels, cochlear implant

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Evaluation of vestibular function in children after cochlear implantation

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Abstract

- Introduction:
Cochlear implants are intended to treat severe to profound sensorineural hearing loss. They are auditory rehabilitation devices designed to restore or develop oral communication. Despite a well-coded surgical procedure, the occurrence of certain complications is not exceptional: Vertigo is the main reported side effect.
- Objectives:
- To describe the impact of cochlear implantation on vestibular function.
- To determine the conditions that favor the appearance of vestibular dysfunction postoperatively.
- To evaluate the correlation between the existence of inner ear malformations and the occurrence of this dysfunction postoperatively.
- Material and Method:
This is a mono-centric descriptive study conducted in the ENT-CCF department of the Avicenne University Hospital in Rabat concerning 23 children who underwent cochlear implantation between September 2021 and October 2022.
- Result:
The study includes 23 children including 13 boys and 10 girls, ranging from 3 years to 16 years. The main indication was a non-syndromic prelingual deafness. However, we also found perilingual and postlingual deafness.
We found cases of malformative pathologies: Mondini disease, Waardenburg syndrome, Gusher syndrome, Usher syndrome, CACH syndrome, branchio-oto-renal syndrome and finally an atresia of the external ear.
All of our patients were evaluated for vestibular function before surgery, and we found only one case of vestibular areflexia. Postoperatively, 3 patients presented an acute vestibular syndrome and no vestibular symptoms were noted after activation.
- Conclusion: The contribution of cochlear implantation, particularly in the pediatric population, is indisputable and its indications continue to expand. However, as with any iatrogenic procedure, its surgery is not without risk, particularly for the vestibular apparatus.

Keywords: vestibular function, cochlear implantation, children

*Speaker

P63

Comparison of the hearing thresholds obtained by auditory brainstem response and auditory steady state response

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Abstract

Background : The diagnosis of deafness and its characterization is the cornerstone of an optimal intervention. The use of ABR and ASSR tools makes it possible to assess the hearing of this difficult to test population. In this study, we tried to compare the ASSR and the ABR in
evaluating the causes of vertigo presenting in ENT outpatient clinics.
Objectives : the comparison between hearing thresholds obtained by the ASSR and those obtained by the ABR reference tool, on a pediatric population suffering from severe to profound deafness
Methods : Our research work is a retrospective comparative study on children who could not be tested by conventional pure-tone audiometry. We thus tested their hearing by two electrophysiological tests: ABR and the ASSR
The study was conducted in the Department of Oto-Rhino-Laryngology and Cervico-Facial Surgery (ORL-CCF) of the University Hospital Center (CHU) Mohammed VI of Marrakech for a
period extended from January 2013 to November 2022 on a population of 35 children with electrophysiological evaluation of their hearing by ABR and ASSR.
Results : In our study, the results of the analysis of the correlations between hearing thresholds measured by ABRs and ASSRs show a strong correlation between these two tools at high frequencies (2 kHz, 4 kHz and their average) and low to moderate correlation at bass frequencies (0.5 and 1 kHz).
Conclusion :
We are convinced that the use of the ASSR in auditory diagnosis is a tool that must be taken into consideration but remains to be correlated with the ABR and audiometry data behavioral.
Funding : None

Keywords: audiology, ENT

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PEA and ASSR correlations (A multicenteric study)

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Abstract

Introduction :
Behavioral auditory tests can be used to assess hearing loss in young children. However, obtaining accurate results in very young children or those with cognitive impairment remains a difficult task. Objective hearing tests are necessary in order to obtain reliable results.

Thus, auditory electrophysiologic tests are all pertinent in these cases, particularly: Auditory evoked potentials (AEP) and the auditory response in steady state (Auditory Steady-state Response ASSR).

This work aims to study the results of ASSR regarding the diagnosis of deafness in young children, by comparing them with those obtained with the use of AEPs.

Material and method :

This is a multicenteric study based on 2 french articles, an Italian article and a Morrocan doctoral thesis in medicine. The study addresses the reliability of ASSR in the diagnosis of deafness in children, comparing its results with those obtained via AEPs.

Results :

All studies claim that ASSRs are as reliable as AEPs in determining a threshold on frequencies 2–4 kHz. In addition, they do not measure latencies, which are not pertinent in the evaluation of deafness in children.

In addition, ASSRs provide information about the hearing thresholds in low frequencies, which are not evaluated by the AEPs.

However, available studies have been carried out on small populations, which means that studies in wider populations are needed.

Conclusion :
The strong correlation found between the hearing thresholds obtained by AEP, with those obtained by ASSR suggest that ASSRs are reliable for the objective assessment of hearing thresholds in children, however studies established on larger populations are needed.

Keywords: PEA, ASSR, Correlation, Young children

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Audiological phenotyping evaluation in KBG syndrome: Description of a multicenter review

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Abstract

KBG syndrome is a rare genetic disorder due to monoallelic pathogenic variations of *ANKRD11*.The typical phenotype includes facial dysmorphism, costal and spinal malformation and developmental delay. Hearing loss in KBG patients has been reported for many years, but no study has evaluated audiological phenotyping from a clinical and an anatomical point of view.
Our objective was to reinforce clinical knowledge of hearing impairment in KBG syndrome.

This French multicenter study included 32 KBG patients with retrospective collection of data on audiological features, ear imaging and genetic investigations.

We identified a typical audiological profil in KBG syndrome: conductive (70%), bilateral (78%), mild to moderate (84%) and stable (70%) hearing loss, with some audiological heterogeneity.

Among patients with an abnormality on CT imaging (55%), ossicular chain impairment (67%), fixation of the stapes footplate (33%) and inner-ear malformations (33%) were the most common abnormalities.

In this innovative study, we have shown that hearing impairment may be the first clinical sign of KBG syndrome and we describe the specific characteristics of hearing loss, underlining the variability of clinical, anatomical and radiological features.
We recommend a complete audiological and radiological evaluation and an ENT-follow up in all patients presenting with KBG. Imaging evaluation is necessary to determine the nature of lesions in the middle and inner ear.

Keywords: Hearing loss – KBG syndrome – stapes fixation – ANKRD11

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Classification of inner ear malformations

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Abstract

I.Introduction:
Internal ear malformations result from an interruption in the inner ear's development in the first quarter of fetal life. They represent 20% of congenital deafness cases, with a mixed or sensori-neural deafness, generally bilateral and profound.

The diagnosis of inner ear malformations is based on radiological aspect, in the association if CT scan and MRI. The aim of this study was to meet the malformations of the inner ear and their classification thus allowing the clinician to establish a therapeutic strategy for this rare pathology.

II.Material and methods:

This is a multicenteric study, established on five studies presenting malformations of the inner ear with different types of classifications.

III.RESULTS:

Several works have been carried out to establish a classification of inner ear's malformations, they differentiate five main groups: malformations of the cochlea, vestibule, semi-circular canals, internal auditory duct and vestibular aqueduct.

The cochlea: 26% of malformations of the inner ear and almost systematically cause hearing loss. The most common deformations according to Schuknecht and Gacek: Michel's malformation is the most severe , then the f the common cavity, and the incomplete partitions of type I, II, III.

Besides malformations, there is the total absence of cochlea (aplasia) , and the interruptions in the development of the cochlea (hypoplasia).

The vestibule: According to Lagundoye, Martinson and Fajemisin: often associated with other malformations of the inner ear, isolated deformations can occur.

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Semi-circular channels:, can be infra-clinical. The most common deformations are: (a more enlarged semi-circular channel, the lateral vestibular malformation of the side canal; the fusion of several channels; the dehiscence of the upper semi-circular canal. The absence of one or more semi- circular.

The vestibular aqueduct: This anomaly was first described by Valvassori and Clemis, it is often associated with other anomalies of the inner ear. This malformation is not the result of an interruption of the development of the inner ear at a specific time.

IV. Confusion:
There are a wide variety of malformations that complicate diagnosis and management of inner ear malformations. A standardized classification of these malformations makes it possible to predict the prognosis and determine the therapeutic scheme to be applied.

Keywords: Inner ear malformations, cochleovestibular malformations, classification .

P67

Epidemiologic profile of children sensorineural deafness in Marrakech.

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Abstract

Background:
Deafness is the most frequent sensory handicap of children. The knowledge of its epidemiology and the establishment of an etiological diagnosis is an essential step that has major prognostic and therapeutic implications.

Objective:

The objective of this study is to determine the epidemiological and etiological profile of sensorineural hearing loss of children in Marrakech.

Methods:

We conducted a retrospective study of the different causes of sensorineural deafness in any child under 15 years of age with at least moderate deafness in the better ear, managed at our training level between January 2012 and December 2020 having identified 399 cases of deafness.

Results:

The average age at diagnosis was 4.2 years and 54.4% of patients were female. Delayed language acquisition and behavioral problems reported by parents were the most frequent reasons for consultation, representing 82.8%. The deafness was prelingual in 79% and bilateral in 87.5%. Consanguineous families represented 49.7% of the total sample. 80.2% had profound or total hearing loss. The deafness was acquired in 35% of the cases, out of the remaining 260 cases 100 children underwent a genetic study which confirmed the genetic cause of their deafness in 22% of the cases.

The hearing loss was of unknown cause in 43% of cases. Among the genetic causes, syndromic deafness represented 21.4% and non-syndromic deafness 78.6%. Autosomal recessive deafness was predominant in 91.2% of cases. The main etiologies of acquired deafness were otitis (29%) and meningitis (22%).

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Conclusion:

The study of childhood deafness is of great public health importance. The impact of deafness on communication and language development depends on the profundity of the deafness and the speed of treatment, hence the need for a positive and etiological diagnosis as early as possible.

Keywords: Sensorineural hearing loss, Epidemiology, children hearing loss.

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Screening for neonatal hearing loss at UHC Mohamed VI of marrakech

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Abstract

Deafness is the most common sensory deficit. It affects about 1 to 2 newborn per thousand births. with a prevalence over 1-4% of the newborn at risk. In order to reduce the dramatic consequences of such a handicap, several screening techniques allowing an objective, reliable and rapid assessment of the functioning of the ear and auditory pathways have been developed in order to offer newborn screening for deafness.
Among them, the OAE and ABR automated techniques that we will be using in our study. Screening will be done at delivery facilities, paediatric intensive care units

Our study is a prospective one conducted in university hospital centre Mohamed the sixt of Marrakech extending for a period of 13 months from January 2022 to February 2023 automated Auditory Evoked Potentials and OAE are two objective and reliable methods of newborn screening

the screening protocol was as follows systematic screening was carried out in the maternity, as well as in the neonatology department for newborns with increased risk factors

Consisting of a first OEA test if the test is negative a second OEA test is carried out after 40 days if the second test is negative, an additional ABRa is performed, in the event of a negative ABRa, the child is scheduled for a ABR under GA

the screening carried out in the neonatology department revealed 240 cases, with a death rate of 11%,

the remaining was 218 of which 58% had a 1st OEA negative, when summoned for the 2nd test only 24% of the cases had a control and PEA negative , 51% which became positive, 9% of deaths and 6% did not present for the control

Thus we are left with 30 patients who are scheduled for PEA under GA of which only 6 are eligible, the rest of the patients have multiple associated defects that made general

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anaesthesia difficult and are scheduled after their general condition has improved

the screening carried out in the maternity ward, which was conducted from 08 January 2023, had 280 cases, of which 95% were negative,

A recontol is currently underway for the negative patients, but the main difficulty that the screening team had encountered was the large number of people lost for multiple reasons which differ from the refusal of the family to go to the test, the geographical distance from the hospital associated with the high cost of travel without forgetting the false phonenombre

the percentage of non-respondents or those lost to follow-up rises to around 45%.

As for the re-testing, we are currently in the first month of re-testing with 44 completed, and the percentage of positive control by AEO or AEP has been 93%, so only 3 patients had 2 negative AEO and one negative AEP are planned for AEP under GA

Thanks to the national protocol of neonal deafness screening , Morocco is on the right track in terms of hearing loss, without forgetting the Lalla Salma association, which plays a pioneer role by giving access to the CI

Keywords: neonatalscreennng, OAEautomatic ABR, hearing loss

P69

Predictable sequential structure enhances auditory sensitivity

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Abstract

The ability to detect even faint audible events at a distance is crucial for efficient reactions. Human hearing is highly sensitive and allows us to detect acoustic events at low levels and at great distances. However, sensitivity is not only a function of the integrity of sensory hair cells, but also constrained by central processes such as attention and expectation. While the effects of distraction and attentional orienting are generally acknowledged, the extent to which probabilistic expectations influence sensitivity is not clear. Classical audiological assessment, commonly used to assess hearing sensitivity, does not distinguish between bottom-up sensitivity and top-down gain/filtering. In this study, we aim to decipher the influence of various types of expectations on sensitivity and how this information can be used to improve the assessment of sensitivity to sound. Our results raise important questions regarding common practices in the assessment of sound sensitivity, both in fundamental research and in audiological clinical assessment.

Keywords: pure, tone audiometry, normal hearing, sequential predictions, top, down

*Speaker

P70

Study of hearing loss in pilots

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Abstract

I

INTRODUCTION:

Pilots are exposed to potentially harmful noise levels. We determined the audiometric profiles of pilots according to age and type of aircraft (fighter, transport, helicopter) and looked for risk factors for hearing loss other than noise in a population of pilots.

METHODS:

We examined 87 pilots between the ages of 30 and 50 during their annual medical visits. The pilots were interviewed using a standardized questionnaire and audiogram data from both ears was collected. Hearing levels were compared between age groups and aircraft category.

RESULTS:

Abnormal hearing levels in the pilots were found mainly at high frequencies with a marked notch on the 6 kHz audiograms. Left ears had significantly lower performance than right ears. At a given age, transport pilots had, on average, better hearing at 8 kHz than other pilots, despite having more flying hours. In addition to the notch at 6 kHz, helicopter pilots showed significant hearing loss at 3 kHz. Such widening of the degraded frequency range may interfere with voice communication.

CONCLUSION:

Pilots flying fighter jets and helicopters are at higher risk of hearing loss than pilots flying transport aircraft. Improving hearing protection seems particularly necessary for the left ear. Hearing loss can potentially compromise voice communication in helicopter pilots.

Keywords: Pilote surdité

*Speaker

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