Hearing loss in children

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ABBREVIATIONS:

CHL:	Congenital hearing loss
DOHL:	Delayed Onset Hearing Loss
AHL:	Acquired Hearing Loss
SHL:	Sensorineural Hearing Loss
CHL:	Conductive Hearing Loss
MHL:	Mixed Hearing Loss
TORCH:	Toxoplasmosis, Others, Rubella, Cytomegalovirus, Herpes Simplex Virus
MMR:	Measles, Mumps and Rubella
CMV:	Cytomegalovirus
AOM:	Acute Otitis Media
URTI:	Upper Respiratory Tract Infection
RAOM:	Recurrent Acute Otitis Media
OME:	Otitis Media with Effusion
ASSR:	Auditory Steady State Response
ABR:	Auditory Brainstem response
CSOM:	Chronic Suppurative Otitis Media
CT:	Computed Tomography
MRI:	Magnetic Resonance Imaging
RP:	Retraction pocket
PCR:	Polymerase Chain Reaction
BOA:	Behavioural Observation Audiometry
OAEs:	Otoacoustic Emissions
AABR:	Automated Auditory Brainstem Response
NICU:	Neonatal Intensive Care Unit
TA:	Tonal Audiometry
FM:	Frequency Modulated

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ABSTRACT

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Hearing loss in children has multiple aetiologies, making diagnosis based on clinical signs and symptoms challenging. Hearing loss at a young age will affect a child's cognitive and linguistic development, resulting in loss of quality of life and possible behavioural and social problems. It is important to screen before the end of the neonatal period, 1 month of age, as well as a follow up at 3 months, due to multiple progressive hearing loss causes. Congenital, delayed onset or acquired hearing loss in children is classified into timing of onset of symptoms. Genetic, non-syndromic, syndromic, and infectious causes are the most common aetiologies. Further characterization of hearing loss based on the mechanism of the auditory system involved yields conductive, sensorineural, and mixed hearing loss. The organisation of different sound frequencies in the auditory cortex ends at 2 years of age and indicates an important window period for intervention. The evidence of benefit from early application of hearing aids and cochlear implants supports the argument to treat and rehabilitate children early.

Keywords: Hearing loss, children, otitis, sensorineural, conductive

SAŽETAK

Gubitak sluha kod djece

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Gubitak sluha kod djece ima višestruku etiologiju, što otežava dijagnosticiranje na temelju kliničkih znakova i simptoma. Gubitak sluha u mlađoj dobi utjecat će na djetetov kognitivni i jezični razvoj, što će rezultirati gubitkom kvalitete života i mogućim socijalnim problemima te problemima ponašanja. Važno je pregledati dijete prije kraja neonatalnog perioda, mjesec dana starosti djeteta, te ponoviti pregled sa tri mjeseca života, zbog višestrukih progresivnih uzroka gubitka sluha. Kongenitalni, postepeni ili stečeni gubitak sluha u djece klacificira se obzirom na početak simptoma. Genetski, nesindromski, sindromski i zarazni uzroci najčešće su etiologije. Daljnja karakterizacija gubitka sluha temeljena na organizaciji slušnog sustava otkriva provodni, senzorineuralni i mješoviti gubitak sluha. Sazrijevanje različitih zvučnih frekvencija u slušnom korteksu završava u dobi od 2 godine i ukazuje na važno vremensko razdoblje za intervenciju. Dokazi o koristi rane primjene slušnih pomagala i umjetnih pužnica jasno pokazuju da je liječenje i rehabilitacija potrebna prije nego što je prekasno

Ključne riječi: Gubitak sluha, djeca, otitis, senzorineuralni, provodni

INTRODUCTION

Hearing loss in children is a common disorder, with 1 in 5 affected in the United States and the United Kingdom by the age of 18 years old (1). Currently hearing loss is defined as any deficit of the ability to hear sounds that should be perceived at normal levels. Childhood hearing loss can be classified according to the timing of hearing loss, namely congenital, delayed onset or acquired. Congenital Hearing Loss (CHL) is attributed to causes present at birth, until 28 days after. Delayed Onset Hearing Loss (DOHL) is recognized after the neonatal period but attributed to causes identified at birth. Lastly, Acquired Hearing Loss (AHL) is detected after the neonatal period and is linked to causes absent at birth (2).

This can be a debilitating disorder because the first 3 years of a child's life is a well-established critical period for cognitive and linguistic development (3). Social and behavioural development has been established to be affected negatively by hearing loss (4). Early detection of hearing loss enables quick intervention, allowing children to develop similar to their hearing peers in linguistic and intellectual performance. Unfortunately, those who are not detected or discovered later will suffer in the abovementioned categories. To address this issue the National Institutes of Health is recommending new born hearing screening within the first 3 months of a child's life (5).

The severity of hearing loss is graded from slight to profound across multiple frequencies. Slight hearing loss is defined as an average hearing threshold of more than 15dB. Mild hearing loss is diagnosed at hearing thresholds 26 dB to 40 dB, moderate at 41 to 55 dB, moderately severe at 56 to 70 dB, severe at 71 to 90 dB and profound hearing loss at more than 90dB(6).

ANATOMY AND PHYSIOLOGY OF HEARING

The ear is made out of three major components: The outer ear, middle and inner components. The outer ear encompasses the pinna to the tympanic membrane, including the auditory canal. Sound waves, made up of variable frequencies, are picked up by the pinna and channelled into the external auditory meatus. Sound waves are focused upon the tympanic membrane, which forms the barrier between the outer ear and the middle ear. For the vibrations to be directed effectively to the inner ear, the pressure on both sides of the tympanic membrane needs to be equal. The eustachian tube ventilates the middle ear, creating equal pressure in the middle ear and in the outer ear. The eustachian tube connects the middle ear anteriorly to the nasopharynx (7).

Middle ear begins from the medial side of the tympanic membrane and includes the ossicular chain and its three components, namely Malleus, Incus and Stapes. The tympanic membrane transmits low frequency waves to the ossicular chain. The ossicular chain converts low frequency sound waves into high frequency and then transmits these vibrations onto the oval window via the stapes(8). The oval window is the beginning and also the most lateral part of the cochlea.

The Cochlea is the anatomic origin of the inner ear and ends at the attachment of the vestibulocochlear nerve. Inside the cochlea the vibrations are not conducted via air anymore, but rather through fluid pressure waves. The waves affect hair cells inside the cochlea found upon the basilar membrane, which are then transmitted into neural impulses (9). The basilar membrane is separated by two different types of fluid namely endolymph and perilymph. Endolymph is similar to intracellular fluid and perilymph can be likened to cerebrospinal fluid. The difference in the chemical fluids creates a membrane potential across the basilar membrane. The intensity of sound

transmitted by the hair cells into neural impulses is determined by the amount of hair cells triggered, with louder sounds recruiting more hair cells.

The vestibulocochlear nerve is responsible for transmitting impulses via brainstem and ultimately to the auditory cortex for additional interpretation. Different sound frequencies are arranged spatially in the auditory cortex. The sounds are organized linearly in relation to hairs cells of the Organ of Corti and its frequency-specific neurons. Organization of different sound frequencies in the auditory cortex is called tonotopy. The maturation of tonotopy starts at 6 months of life and is finalized at 24 months. Importantly, this defines a critical period for intervention of any types of hearing loss and its correction(9).

TYPES OF HEARING LOSS:

Any part of the auditory system can be affected leading to several types of hearing loss. The division of hearing loss is attributed to the location of the pathology. Three main types of hearing loss are: Conductive, Sensorineural, and Mixed.

Sensorineural Hearing Loss (SHL) can be produced by any pathology within the cochlea, cochlear nerve or its path to the auditory cortex (10).

Conductive Hearing Loss (CHL) is characterized as any pathology of the external or middle ear components, including the pinna, external auditory canal, tympanic membrane, ossicles, or middle ear space (11).

Lastly, Mixed Hearing Loss (MHL) is defined as any mixture of Sensorineural and Conductive types of hearing loss.

CONGENITAL HEARING LOSS

Hearing loss is most commonly sensorineural in children, with a prevalence of 1-2 per 1000 births (12). Half of all SNHL cases in the congenital period is attributed to genetic causes, often producing bilateral hearing loss. Furthermore, 70% of genetic causes are considered to be non-syndromic and 30% are syndromic.

Structural abnormalities of the temporal bones are the second most common cause of SNHL (30-40%) producing unilateral hearing loss more frequently. Anatomical abnormalities frequently present as a component of syndromes, such as Waardenburg, Branchiootorenal and CHARGE syndrome (13). Irregularities of the internal auditory canal, cochlea or vestibular apparatus have been described in increased likelihood in children with SNHL and a congenital syndrome simultaneously present (14).

Congenital infections, namely TORCH (Toxoplasmosis, Others, Rubella, Cytomegalovirus, and Herpes Simplex Viruses) infections, are present in varying degrees in congenital SNHL (5-20%) (15). Cytomegalovirus (CMV) is most common detected pathogen of the TORCH infections, often resulting in a profound and bilateral hearing loss. Congenital Rubella used to be a common viral aetiology of SNHL, has been significantly reduced due to the introduction of the MMR (Measles, Mumps, Rubella) vaccination. Congenital Syphilis, thought to be a worry of the past, has seen increasing numbers the past few years (16).

Between 25-40% of SNHL causes in the congenital period remains unidentified. However, other risk factors have been identified. Prematurity and low birth weight increase risk for developing CHL. Up to 7.5% of infants in Neonatal Intensive Care Units (NICU) develop hearing loss, due to risk factors linked to low gestational age. Identified risks factors are hypoxia during birth, prolonged ventilation, hyperbilirubinemia, sepsis, bacterial meningitis and extracorporeal membrane oxygenation (2).

DELAYED-ONSET HEARING LOSS

DOHL could occur if a child has a positive history for a congenital CMV infection or stayed in the NICU for more than 5 days in the congenital period. Concern must be risen about children with delays in linguistic development. Hundreds of genes have been identified to cause SNHL or MHL. Syndromes attribute to many of the genetic causes and often produce a DOHL, often proving to be a progressive loss of hearing(17).

Pendred syndrome is connected to the SLC26A4 gene and presents as a SNHL with recessive inheritance. Feature of Pendred syndrome includes goiter with thyroid

dysfunction, enlarged vestibular aqueduct and an intracochlear partition defect type II(18). Another recessive genetic syndrome called Usher syndrome has 3 clinical types and is linked to 9 genes with varying degrees of hearing loss progression, as well as vision impairment and vestibular dysfunction.

Alport syndrome can be either an X-linked (in most cases) or a recessive gene linked syndrome that leads to glomerulonephritis and ultimately kidney failure. Ocular retinopathy and a progressive SNHL which is usually detected later in childhood are common features of Alport syndrome (19).

Many genetic causes of SNHL are non-syndromic, with initial newborn hearing screenings proving no deficit. However, because of the progressive nature the hearing loss becomes much worse as the child ages. Connexin 26 associated with gene GJB2, STRC and MY015A are a few of the common recessive genes identified. TMC1 and KCNQ4 are some of the autosomal dominant genes associated with progressive hearing loss (20).

TORCH infections in the prenatal period can result in DOHL, being more prominent in the past. Currently, congenital CMV is the only significant cause of DOHL worldwide, with a prevalence of up to 2.3%. The progressive nature of the hearing loss caused by CMV will enable to child to pass newborn hearing screening, only to present later in childhood with a SNHL (21).

Other TORCH infections that could result in DOHL of sensorineural nature includes toxoplasmosis and syphilis. Recent reports have identified the Zika virus as a cause of hearing loss in North and South America (22).

ACQUIRED HEARING LOSS

Many causes of childhood hearing loss can be attributed to preventable causes such as infection, trauma, ototoxic medications, and autoimmune diseases. Infectious aetiologies have been postulated to be involved in 30% of AHL cases (23).

Common infectious and acquired causes like Acute Otitis Media (AOM), Otitis Media with Effusion (OME), Chronic Suppurative Otitis Media (CSOM), Retraction Pocket (RP) and Cholesteatoma will be discussed separately in this review due to their clinical complexity.

SNHL caused by infections include measles, mumps, varicella zoster and bacterial meningitis, with measles and mumps infections preventable with vaccination (24). Streptococcal meningitis could result in SNHL due to progressive labyrinthine ossification; these patients must receive cochlear implants before it is too late (25).

Trauma to the temporal bone can produce varying types of hearing loss, ranging from CHL to SNHL. CHL can be a result of foreign body in the external auditory canal, wax impaction, otitis externa, tympanic membrane perforation or ossicular chain injury. Temporal bone fractures or concussions can produce a permanent or temporary profound SNHL after injuring the cochlear nerve or the cochlea (26). Excessive noise, louder than 120dB can cause immediate permanent damage to the outer hair cells.

Common ototoxic antibiotics belong to the aminoglycoside group and other drugs like cisplatin and loop diuretics can produce a permanent hearing loss. Other drugs identified to result in a reversible hearing loss are salicylates and macrolides like azithromycin. Therefore, drug and dosages prescribed to children need to be observed carefully to reduce the odds of ototoxicity. Studies have identified genetic

susceptibility linked to aminoglycoside toxicity due to mitochondrial variety in humans (27).

Cogan syndrome is an autoimmune disease with vestibular dysfunction and interstitial keratitis, producing a progressive hearing loss which could be responsive to immunotherapy (28).

Acute Otitis Media

Acute otitis media (AOM) is characterized as an infection of rapid onset and pain localized to the middle ear (29). AOM is the most common infection in young children from 6 to 18 months with a peak incidence around 9 months and less frequently after 3 years of life. Roughly 80% of children have an ear infection before 3 years (30).

Risk factors

AOM is frequently preceded by a present or positive history of an upper respiratory tract infection (URTI), usually a common cold caused by a virus. The eustachian tubes becomes clogged by mucus or fluid, preventing the middle ear form being drained. The immune system is not fully developed in children, creating an opportunity for bacteria to flourish causing a localized infection in the middle ear space. Anatomically in children the eustachian tube is much shorter and more horizontal than in adults, further impeding outflow into the nasopharynx. Children also have enlarged adenoid vegetations adding to the outflow problem. Other risk factors for AOM is tobacco smoke exposure, day care attendance and atopy (31).

Causes

Secretions in the nasopharynx caused by viral infections, strep throat or allergies can be aspirated into the eustachian tube. Various types of bacteria have been identified from these secretions. The most frequent bacteria causing AOM is Haemophilus

Influenzae, with a frequency of 30-40%. 15% of Haemophilus Influenzae creates beta lactamase as well as 8% of this pathogen has reduced sensitivity to amoxycillin (32).

Second most common is Streptococcus pneumoniae identified in 40-25% of cases. 42% of Streptococcal infections in AOM shows reduced sensitivity to penicillin. Third most frequent infective agent in AOM is Moraxella catarrhalis, with a frequency of 10-5%. Other mentionable pathogens are Streptococcus pyogenes, Staphylococcus aureus, Corynebacterium, Pseudomonas aeruginosa and Enterobacteriaceae all with a 5% (33).

Diagnosis

Diagnoses of AOM is based on the clinical picture and otoscopic findings. There can be signs and symptoms which are both general and local. The most common symptom is ear pain, which can be accompanied by agitation and crying.

Fever is often present with Streptococcal infections producing a temperature of more than 38.5°C in half of the cases. The skin superior to the pinna can be sensitive to touch (34). Drowsiness, sleep disturbances, loss of appetite, vomiting and diarrhoea are more common symptoms in young children. Nasal secretions and cough can be present due to a current URTI.

Otoscopic findings for acute otitis media are diagnostic. The manubrium of the malleus will not be visible. The triangular glare, otherwise known as “the cone of light”, is usually visible when light is shone on a normal eardrum, will be absent. Finally, and most importantly, tympanic membrane bulging will be visible. Bulging of the tympanic membrane is an important differentiating sign between AOM and Otitis Media with Effusion (OME), as OME does not require antibiotic treatment (35).

Prevention/Vaccination:

In order to prevent the most common cause AOM, S. pneumoniae, a 7-valent pneumococcal conjugate vaccine (Prevenar7) has been researched. Initially it was created to combat pneumonia but has been shown effective, by decreasing childhood frequency of AOM in both USA and Canada. Specifically reducing AOM incidence in children under 2 years by 43%, as well as a decrease in antibiotic treatment requirements (36). Prevenar7 showed a significant increase in S. pneumoniae and atypical strains of H. Influenzae caused AOM.

The 13- valent vaccine (Prevenar13) is currently the main recommended immunization. Presently, A 23-valent (Pneumo23) vaccine has been developed. Displaying a reduction of S. pneumoniae AOM, however there is no data on whether the absolute number increases or only the percentage of cases of infection with H. influenzae and M. catarrhalis (37).

Complications

Intracranial complications of AOM can be life threatening with vital structures surrounding the middle ear space, namely the meninges and brain superiorly and the sigmoid sinus located posteriorly. If the AOM spreads it can lead to sigmoid sinus thrombosis, meningitis, subdural-, epidural- and brain abscesses.

Extracranial complications can be common as well, with acute mastoiditis topping the list. The mastoid periosteum becomes inflamed directly from a spreading AOM infection, presenting with post-auricular swelling and mastoid tenderness aside from other typical AOM symptoms. This type of infection is more common in children under 2 years of age, with an incidence of 1.2-6 in 100,000 (38).

Treatment

Most acute ear inflammation passes without antibiotics and treatment is based on adequate analgesia, antipyretics and solving obstruction of the nose and nasal pharynx. Research has shown that 80% of children will spontaneously resolve an AOM infection within 2-14 days (39). However, in children younger than 2 years the rate of spontaneous resolution is less than 30%. Analgesics and antipyretics should be administered in the first 24-48 hours. Drugs preferred by the European National Guidelines are a combination of ibuprofen (10 mg per kg every six hours) and acetaminophen (15 mg per kg every four to six hours). As well as Tramadol drops, which can be administered for 3-year-olds and above (40). Rhino pharyngeal hygiene habits can decrease AOM incidence, like educating children to blow their noses often and rinsing the sinuses with isotonic and hypertonic solutions.

Children older than 2 years with mild symptoms should not receive antibiotics as well as children aged 6 to 23 months with a mild unilateral AOM. Symptomatic treatment should be given, and re-evaluation should be performed after 48h to 72h is there is persisting symptoms. If persisting symptoms are present, then Amoxicillin should be administered.

Antibiotics should be administered in children older than 6 months with severe unilateral or bilateral AOM. Severity is defined by intense otalgia, lasting more than 48 hours and an increased temperature of 39 degrees Celsius (41). First line antibiotic for children older than 2 years of age with uncomplicated AOM is Amoxicillin 80 to 90 mg per kg per day, divided into two doses for 5 to 7 days. A 10-day course is prescribed to children between 6 and 23 months old (39).

If the patient has taken this antibiotic in the last month or is allergic to penicillin, then Cefuroxime 30 mg per kg per day for 10 days or Ceftriaxone 50mg per kg per day for 3 days, can be administered. If there is any contraindication for beta lactams, then Azithromycin for 5 days can be administered (42). In treatment, there are national and international guidelines that must be renewed at least every 10 years and adapted to microbiological evolution and the creation of resistance to individual antibiotics.

Important to note that if a patient has three or more AOM episodes in a 6-month period then Recurrent Acute Otitis Media (RAOM) is diagnosed. First line treatment of RAOM is surgical tympanostomy with ventilation tube insertion, as seen in Figure 1. The ventilation tube will naturally be expelled over a period of 12 months as the tympanic membrane heals

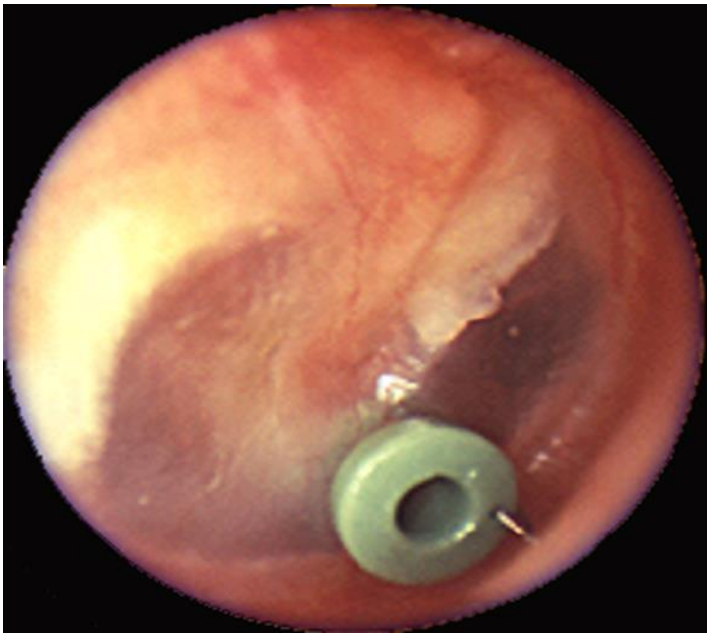

Figure 1: Ventilation Tube in Tympanic Membrane. Photo taken by Asst. Prof. Lana Kovač Bilić

Otitis media with effusion (OME)

Secretory otitis media, or more commonly known as Otitis media with effusion (OME), may be a result of an inflammatory response after an episode of AOM, URTI or due to eustachian tube dysfunction. OME is characterized by a glue-like fluid, behind an unruptured tympanic membrane for more than three months, in the absence of signs of an acute infection. Hence OME being referred to as “glue-ear” colloquially. More than 60% of children will experience an episode of OME before 2 years of age (43). Schoolchildren aged 6 years old were screened for OME and 12.5% had positive signs of OME (44).

The histological chronic inflammatory state in the middle ear causes the mucosa to become inflamed leading to an increased production of viscous mucin. The thick mucin accumulates in the middle ear and blocks the eustachian tube. OME has been linked to URTI’s, smoke exposure and atopy. Other predispositions thought to attribute to the pathogenesis of OME are changes in muco-ciliary transport, metaplasia in the secretory epithelium and changes in transepithelial transport, all exacerbated by smoke exposure. Genetic factors have been identified with increased prevalence of OME in the same family, affecting the host immune function through influences on regulators of inflammation (45).

OME development is influenced by environmental temperature, with an increased prevalence in summer as opposed to winter. Nursery exposure is associated with a 2-and-a-half-fold increased risk. Host risk factors contributing to OME development are sex (males more often than females), immune deficiency (IgA, IgG2 deficiency), short-term breastfeeding, iron deficiency, premature born and ciliary dyskinesia (Kartagener syndrome). Laryngopharyngeal reflux of stomach contents into the middle ear space contributes to inflammatory state, with pepsin often identified in the

effusion. Anatomical risk factors for OME are adenoid hypertrophy or craniofacial malformations like cleft palate, di George, Pierre Robin, Crouzon's disease, or Down's syndrome (46).

The most common reported symptom is hearing loss due to non-infected fluid in the middle ear space for a period of more than three months. As well as reporting a feeling of fullness in the ear. OME will achieve spontaneous resolution within three months, however if it extends this period then there is a risk of conductive hearing loss developing, due to loss of tympanic membrane mobility. Other complications of untreated OME are retraction pockets and tympanosclerosis.

Therefore, a period of watchful waiting is recommended, and treatment should only be considered once a persistent effusion is identified. In the developed world OME has been identified as the most common cause of hearing loss in children (47).

Diagnosis

Commonly children with OME are asymptomatic and are detected on routine screenings. Children rarely complain about hearing difficulties; parents may complain about speech development delay, behavioural problems, sleeping disturbances like snoring and mouth breathing. Other visible signs are loss of balance or clumsiness and a withdrawn nature of the child (48).

Otoscopy performed by an ENT specialist is diagnostic in around 78% of cases with 95% specificity. As seen in Figure 2: Otoscopic findings for OME will present with a visible manubrium of the malleus. The middle ear fluid may be golden and air bubbles will be visible if the patient is able to ventilate the middle ear space with the Valsalva manoeuvre. Nonspecific findings will be an absent triangular glare as well as no tympanic membrane bulging (35).

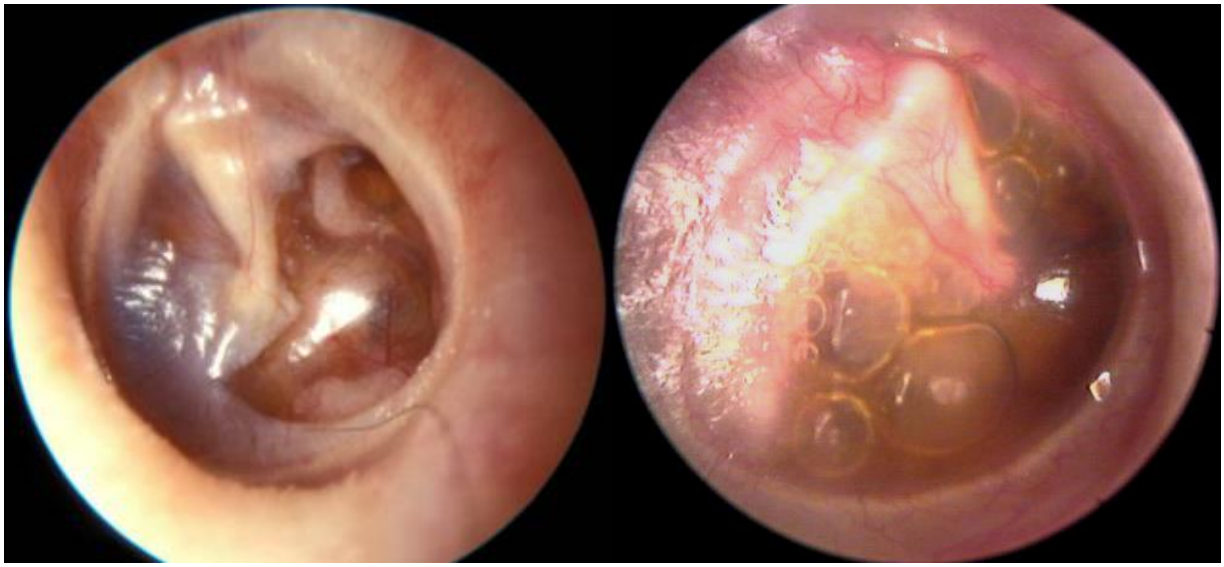

Figure 2: Otoscopy of OME. Photo taken by Asst. Prof. Lana Kovač Bilić

Tympanometry aids in the diagnosis of OME. The compliance of the eardrum is measure by placing a probe inside the ear canal and emitting soundwaves. The tympanic membrane's response is measured by the sound waves it reflects back to the probe. A healthy eardrum will reflect soundwaves, drawing a peaked tympanogram. In OME the fluid behind the eardrum absorbs the soundwaves resulting in a flat tympanogram graph (48).

Further investigations will include tonal audiometric testing (air and bone conduction) to establish if any hearing loss is present. Most commonly OME produces a mild-to-moderate (0-55dB) conductive hearing loss at speech frequencies of 500 Hz to 4 kHz, however normal hearing thresholds may be present with abnormal auditory processing (49). The preferred method of audiometry is dependent on the age of the patient. Behavioural observation audiometry is recommended for patients younger than 6 months. Visual reinforcement audiometry is used for children 6 months to 2.5 years old and children older than 2.5 years old are assessed by play audiometry.

Children 4 years and older undergo conventional audiometry with hand raising when hearing different frequencies.

Treatment

Most children resolve their effusion within a month and a half spontaneously, therefore no immediate treatment is recommended. A period of observation is preferred, with children older than 2 years old seen at 3-month intervals.

Auto inflation, otherwise known as the Valsalva manoeuvre, has been identified as an effective and low-risk home remedy. Antihistamines, steroids, and decongestants have been proven to show no benefit with multiple adverse effects. Surgical intervention is considered after 3 to 4 months of OME with a 20 dB or greater loss of hearing.

Tympanostomy with ventilation tube insertion is currently the standard surgical treatment. The ventilation tube will extrude naturally over a period of 12 months as the tympanic membrane heals. Ventilation tubes reduce incidence of acute middle ear inflammation in children under 3 years of age. Secretion from the ear (otorrhea) after installing ventilation tubes is treated locally with antibiotic drops, quinolones are preferred. Ventilation tubes play a preventive role in the formation of chronic inflammation of the ear with cholesteatoma (50).

Myringosclerosis (10%) and localised eardrum atrophy (14%) are more common after installation of tubes. Myringosclerosis is a structural change in eardrums and does not affect the situation in the middle ear and localised eardrum atrophy can only rarely lead to a retracting pocket and/or cholesteatoma (51). The iatrogenic complications of installing ventilation tubes are very often associated with the

progression of the underlying disease, which must clearly be explained to parents preoperatively.

Adenoidectomy is recommended in children over 4 years of age if adenoid hypertrophy is identified by fiberscope or during the installation of tympanostomy with ventilation tube insertion. Additionally, symptomatic obstructive adenoid hypertrophy in children under 4 years age indicates an adenoidectomy. Special caution is recommended in children with craniofacial malformations with monitoring every 6 months until 6 years of age, thereafter a yearly follow up is sufficient (52). Finally, adenoidectomy with ventilation tubes is recommended in children older than 7 years of age with chronic effusions caused by conditions like allergies and laryngopharyngeal reflux.

Audiometric treatment should be performed after treatment of OME in children who have delayed speech development, problems in school, balance problems and a moderate to severe hearing threshold before treatment.

It is recommended to perform Auditory Brain Response (ABR) or Auditory Steady State Response (ASSR) after installing ventilation tubes if audiometry cannot be done, especially in younger children, or the findings of audiometry are extremely poor (9). Speech therapist treatment is recommended only after treatment of OME in children with preoperative suspicion of delayed speech development and reading.

Chronic Suppurative Otitis Media

A perforated tympanic membrane with continual otorrhea from the middle ear space for a period longer than 2-6 weeks is diagnosed as chronic suppurative otitis media (CSOM). CSOM is otherwise known as chronic otitis media or chronic mastoiditis, due to its persistent infection of the middle ear space, mastoid cavity, or both (53).

The main symptom of CSOM is loss of hearing in the involved ear with a mild to moderate hearing threshold of 26-60 dB, however if the perforation closes naturally there could be no hearing loss detected. Discharge from an ear affected by CSOM can range from putrid or purulent to clear. The external ear canal could be swollen as well. Other symptoms include fever, vertigo, and pain. The middle ear mucosa, visualized through a perforated tympanic membrane, as seen in Figure 3, may be thickened and granular with mucosal polyps present. There is an association with CSOM and the development of cholesteatoma, both of which can be present simultaneously due to their similarity in developmental conditions (54).

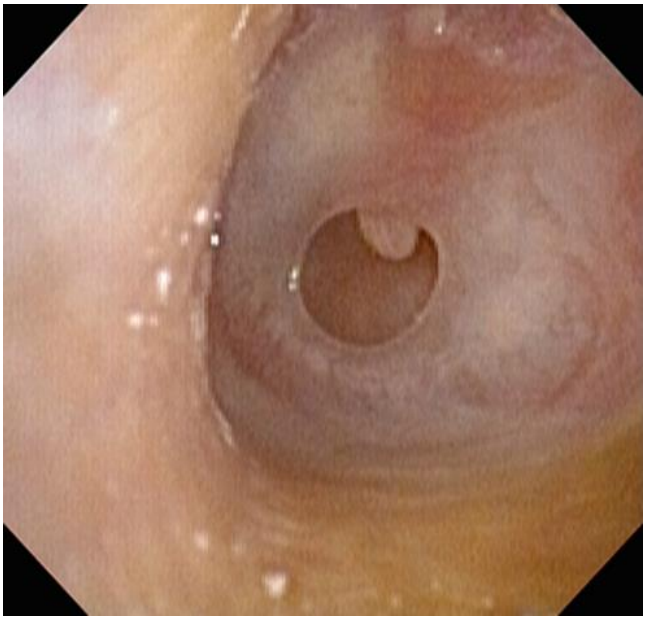

Figure 3: Tympanic Membrane perforation. Photo taken by Asst. Prof. Lana Kovač Bilić

Complications of CSOM are not seen often, largely because of antibiotic treatments available. Nonetheless, similar complications as seen in AOM are possible. Meningitis, thrombophlebitis, and intracranial abscesses are most the threatening. Other complications include labyrinthitis, facial paralysis and petrositis. Hearing can be affected by tympanosclerosis and acquired cholesteatoma which are sequelae of CSOM (54).

Diagnosis

Diagnosis of CSOM is prioritised by acquiring a culture in order to identify bacterial types and sensitivities. Firstly, Pseudomonas aeruginosa and secondly Staphylococcus aureus are the two most frequently cultured bacteria from CSOM secretions. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans are only recommended when no improvement is seen with antibiotic treatment as well as when there is high clinical suspicion of complications.

Performance of audiometry is recommended before any surgery, with conductive hearing loss most commonly present. If an ossicular chain pathology is present large air-bone gaps will be present on a high frequency audiogram with a sensitivity of 83% and a specificity of 92% (11). Presence of sensorineural or mixed hearing loss can indicate progressive disease and is a distressing sign of possible complications.

Treatment

Topical antibiotics is the preferred treatment. Otic drops containing ciprofloxacin with hydrocortisone can be applied twice daily, 3 drops at a time for 7 days. Another option is applying 4 drops of a mixture of Neomycin and hydrocortisone 3 to 4 times

daily for period of 7 days. However, with aminoglycoside antibiotics vestibular and cochlear toxicity should be monitored (55).

In order to allow adequate topical antibiotic penetration, it is crucial to clean the external auditory canal with a technique called aural toilet. This is performed with a microscope and micro instruments in order to mechanically eradicate wax, excess skin, and exudates. A half acetic acid and half sterile water solution is used to irrigate the external auditory canal (56). Systemic therapy is applied if topicals fail, with oral fluoroquinolones being sufficient. Failure is most often due to anatomical barriers caused by cholesteatoma or granulation tissue.

Therefore, surgery is the definitive treatment for most CSOM cases. Tympanomastoidectomy with exploration of the mastoid cavity is performed to eliminate the infection and the persistent otorrhea. An essential part of surgery is to control and remove the granulation tissue inside the mastoid bone and middle ear. Illustrated in Figure 4 below, a tissue graft tympanoplasty, is indicated to repair and close the chronic perforation and treat the underlying cause of hearing loss.

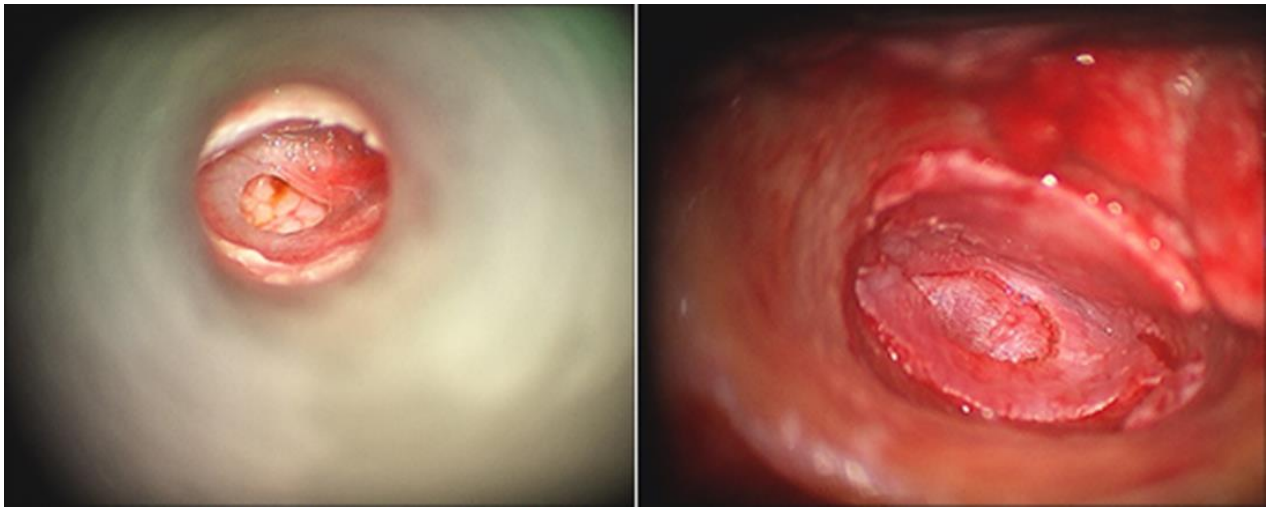

Figure 4: Perforated Tympanic Membrane (Left) and Tissue graft Tympanoplasty (Right). Photo taken by Asst. Prof. Lana Kovač Bilić

Retraction Pocket

Retraction pocket (RP) or otherwise known as tympanic membrane retraction, has a clinical relevance in the formation of cholesteatoma, so early and accurate diagnosis and adequate treatment is crucial in preventing the formation of cholesteatoma of the middle ear. Pathologically a part of the eardrum, pars flaccida, is pulled towards the medial part of the eardrum due to the atrophy of the central, fibrous layer called the pars tensa (57).

RPs frequently occur in patients with a history of tympanostomy tube placement, due to incomplete healing of the fibrous layer. Negative middle ear pressure caused by eustachian tube dysfunction or OME contributes to the pathogenesis of RP development. Up to a quarter of school aged children are affected by RPs with a much higher prevalence in children with cleft palates (58).

Signs and symptoms

Commonly no symptoms are present with retractions, however mild hearing loss can be present due to the decreased mobility of the tympanic membrane. A permanent hearing loss may be present if ossicular erosion develops due to persistent contact of the tympanic membrane. Recurrent or relentless otorrhea indicates development of cholesteatoma from the RP (59).

Diagnosis

Diagnosis is made based on clinical history as well as otoscopic evaluation. As illustrated below in Figure 5 where a retracted eardrum around the lateral process of the malleus will be visible.

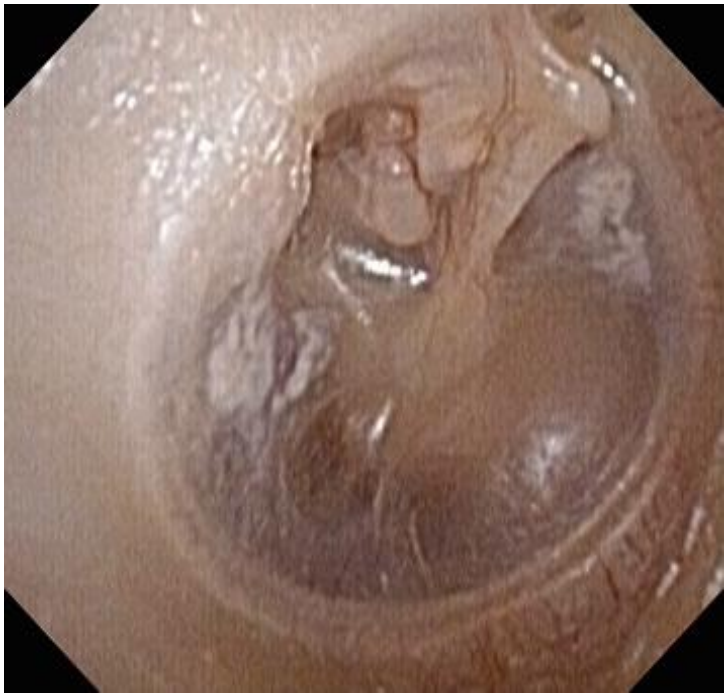

Figure 5: Retracted tympanic membrane. Photo taken by Asst. Prof. Lana Kovač Bilić

Treatment

RPs may be clinically unstable indicating a tendency to resolve or could persist with progression of time. Therefore, it is appropriate to observe for a period before deciding on surgical intervention. In addition to the waiting period, patients can be instructed to perform the Valsalva manoeuvre at home in order to compel the retracted eardrum out of the middle ear space (60).

Decision on surgical treatment is linked to the fact that symptoms present at an early stage as well as in the advanced stage of the disease, may be minimal. Surgery is indicated in advanced stage of the disease with conductive hearing loss and ossicular erosion present. Tympanoplasty with or without ossiculoplasty is the preferred surgical intervention for RP. Excision of the retracted area with reconstruction of the tympanic membrane is performed with a double cartilage plate technique created from a tragal (outer ear) cartilage-perichondrium graft (31).

Cholesteatoma

Cholesteatoma is defined as an abnormal accumulation of keratinized squamous epithelium collected within the middle ear cavity with possible erosion of the temporal bone and local structures. Persistent otorrhea and granulation tissue are frequently associated with a secondary infection of the shedding epithelium (61).

Pathophysiology

Two types of cholesteatoma occur: Congenital cholesteatoma and Acquired cholesteatoma. Congenital cholesteatoma is postulated to develop form residual dermoid tissue in the anterio-superior middle ear space, after failure of reabsorption in embryogenesis (62). Acquired cholesteatoma is theorized to develop from a retraction pocket or a ruptured tympanic membrane, allowing migration of epithelium from the external auditory canal into the middle ear space. However, currently after much research the real pathophysiology of cholesteatoma is still uncertain (63).

Clinical Signs and Symptoms

Recurrent or relentless otorrhea of a painless nature is the most common symptom. Osteolysis cause by local inflammatory conditions can lead to ossicular damage and conductive hearing loss. Additionally, ear fullness and vertigo are possible if the lesion grows to invade the inner ear. Central nervous system signs, namely meningitis and abscesses, may be present in severely progressive cases (64).

Congenital cholesteatoma is a white mass present behind an unruptured eardrum with or without history of ear infections or local surgery. The mean age of congenital cholesteatoma diagnosis is 4-5 years. Recurrence of AOM or otorrhea in the affected ear should be alarming to the physician. The middle ear space, mastoid cavity, petrous bone apex and cerebellopontine angle are the possible locations for

congenital cholesteatoma to be found, with up to 50% of cases located in the cerebellopontine angle (65).

Acquired cholesteatomas can be classified according to three possible locations: Pars tensa, Attic and Tympani sinus with a posterior subligamentary origin. Childhood acquired cholesteatomas most commonly originate from or close to the pars tensa. Notably, retraction pockets are claimed to be involved in the development of cholesteatoma, especially if they are marginally located, fixed outside of the ossicles and possess an uncontrolled nature (61).

Diagnosis

Cholesteatoma is most often detected by careful otoscopic examination, illustrated in Figure 6 below, in children with a history of persistent discharge that does not respond to treatment. CT scanning is indicated as it shows any bone involvement present, namely ossicular erosion, temporal bone, or mastoid space involvement. Preoperative evaluation is planned by CT scanning and MRI imaging can be used if intracranial expansion is suspected. A hearing baseline must be determined before any surgery with audiometric testing.

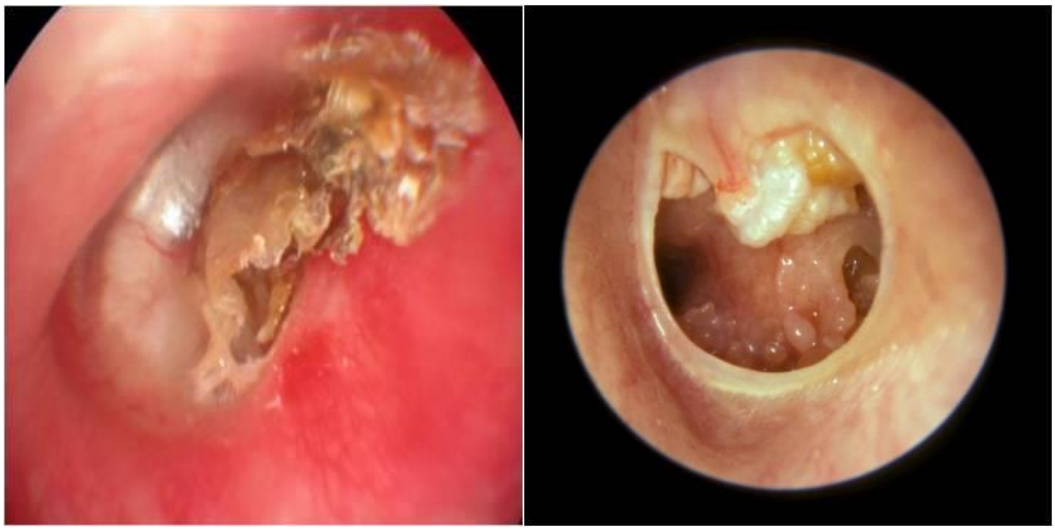

Figure 6: Cholesteatoma. Photo taken by Asst. Prof. Lana Kovač Bilić

Treatment

Usually, most cholesteatoma cases are treated surgically in order to remove the present cholesteatoma. Contraindications to surgery are any patient comorbidities preventing surgical intervention, as well as complete hearing loss in the contralateral ear (66).

Two surgical approaches are popular currently. A canal wall-up approach preserves the canal wall and a normal auricular appearance, however there is a risk of cholesteatoma recurrence. Surgeons will require a follow up mastoidectomy 6 months post operatively to confirm disease clearance.

A canal wall-down procedure or open technique, seen in Figure 7 below, is usually preferred as the disease recurrence rate is substantially lower, with patients generally requiring this procedure only once. Disadvantages of this approach is an enlarged meatus, proving hearing aids difficult to fit. Irrespective of the approach used, it is essential to remove all of the air cells within the mastoid. Furthermore, if the ossicles are affected an ossiculoplasty can be attempted either during the initial procedure or planned later in a second operation (67).

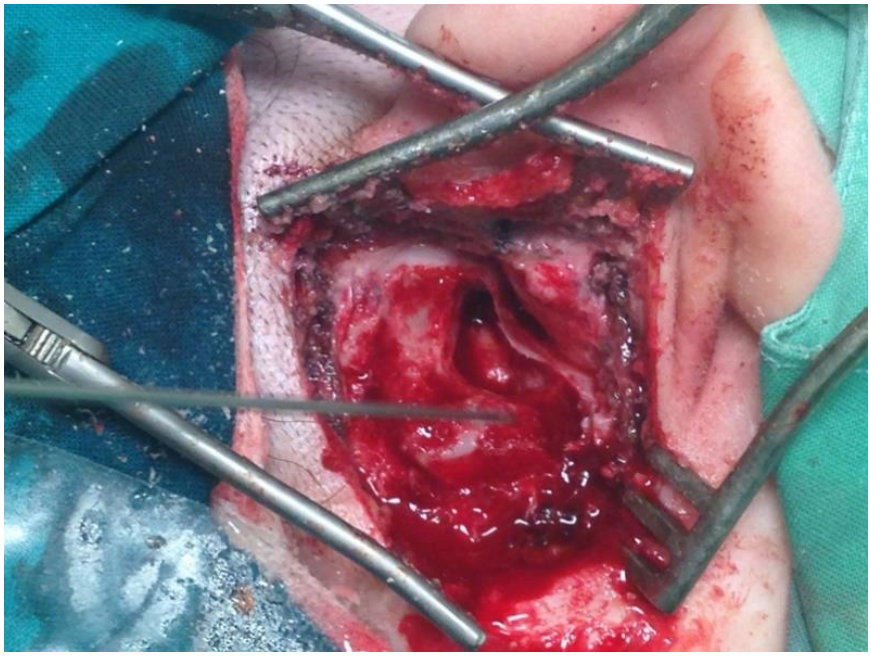

Figure 7: Mastoidectomy. Photo taken by Asst. Prof. Lana Kovač Bilić

Postoperatively the patient should be followed closely to identify any complications. The open or canal wall down-down technique requires packing removal one week after the surgery. In order to battle common gram-negative bacterial infections, namely Pseudomonas, postoperatively fluoroquinolone otic drops are preferred for 10 days a twice daily. Steroid-containing otic drops, like Ciprodex (ciprofloxacin/dexamethasone), are extremely useful in controlling exuberant granulation tissue (61).

DIAGNOSIS OF HEARING LOSS

It is of great importance to rapidly diagnose hearing loss in order to rehabilitate the child maximally with the aim of avoiding speech development deficits. Hearing loss of any type should be assessed based on clinical presentation, family, and medical history. Parameters to consider are patient age, time of onset of hearing loss, unilateral or bilateral symptoms or if the hearing loss is attributed to a syndrome or isolated. Other important details to note are if the hearing loss is transient, permanent or progressive (68).

Newborn screening tests are performed to test for congenital CMV by taking urine, saliva, or blood within first 3 weeks of life. Polymerase Chain Reaction (PCR) testing can detect the presence of CMV within the samples (21). Additionally, other newborn screening tests can include PCR testing for congenital TORCH infections. Lastly and importantly, the physician should always listen to the parent's comments, even in case of normal neonatal screening.

Imaging considerations are CT vs MRI of the temporal bones in order to assess anatomical abnormalities. Importantly, the physician must consider if the risk of exposure to radiation is required. Ophthalmologic assessment can provide information about combined anomalies like CHARGE syndrome. Genetic testing is an important invasive tool used to detect multiple possible syndromic and non-syndromic causes of hearing loss. Unfortunately, results may be inconclusive due to many undiscovered genes involved in hearing loss (18). Urinalysis and thyroid function studies will provide important information on diagnoses, like Alport and Pendred syndrome that should not be missed (19).

Testing Methods for the Diagnosis and Characterization of Hearing Loss

Advances in technology have allowed newborn hearing to be tested more accurately at earlier ages. Behavioural Observation Audiometry (BOA) was used in the past, with the infant (less than six months old) is placed on the parent's lap and presented with tones or speech in various frequencies (69). Responses like head turning towards the sound origin or startle responses are considered as positive responses. However, shortcomings are that the test interpretation requires skilled examiners as well as the test does not assess the ears individually (10).

Now tests like Otoacoustic Emissions (OAEs), Auditory Brainstem Response (ABR) and Automated Auditory Brainstem Response (AABR) provide objective assessment of the auditory pathways with no infant cooperation needed as in behavioural observation audiometry (70). In OAE testing a probe is placed in the ear and produces tone bursts. The outer hair cells in the cochlea produces evoked sounds which are recorded by the probe. The presence of a response indicates a pass (11).

ABR measures the response of the brainstem after transmission of sound signals from the middle ear and vestibulocochlear nerve with electroencephalographic waveforms via electrodes placed on the skin. ABR testing can be used for screening or to detect hearing thresholds (71). AABR is based on the same principle as ABR, however it is used to screen infants in the neonatal intensive care unit (NICU).

Protocols in newborn screening indicates OAE testing of full-term children. If the OAE testing proves a negative result, then a second screening is indicated before 1 month of age. If the second screening turns out negative again, then ABR testing should be performed before 3 months of age (12). Neonates in the NICU commonly

receives AABR testing, with negative results requiring OAE testing and a ABR before 3 months of age.

Tonal Audiometry (TA), or otherwise known as Conventional Audiometry is used to measure subjective hearing thresholds in patients aged 4 years and older. In TA the patient responds to tones at various audible frequencies delivered through headphones or bone vibrators, producing an ear-specific audiogram (72).

Tympanometry measures the tympanic membrane's compliance by the sound waves it reflects to a probe. A normal eardrum will reflect soundwaves, resulting in a peaked tympanogram. Tympanometry is not useful as a test of hearing as well as not indicated for use in newborns. Tympanometry does provide information about the eardrum's function and the status of the middle ear.

TREATMENT OF HEARING LOSS

In order to allow infants to optimally develop spoken language and develop normally compared to their non-hearing challenged peers, they must receive targeted interventions by 6 months of age (73). Younger children are able to adapt to their hearing devices faster with the aim of maximizing their communication and academic abilities.

Hearing devices commonly used in the treatment of childhood hearing loss are Frequency Modulated (FM) Systems, Hearing Aids, Bone-Anchored Implants and Cochlear Implants. Hearing devices are available to treat various types of hearing loss, substituting, or bypassing the affected part of the hearing pathway. The tailoring of hearing devices is a complex process and must be managed by an audiologist.

FM Systems are useful in teaching environments, with the speaker making use of a microphone to transmit sounds to a FM receiver or portable speaker sitting in front of the listener or hanging around their neck. FM receivers can improve the use of hearing aids or cochlear implants by connecting to these devices. FM systems are most useful in noisy environments and when communication is attempted over a longer distance (74).

Hearing Aid is an external device looped over the pinna and fitted into the external auditory meatus. Each hearing aid is fitted personally to each patient. An external receiver detects sounds and amplifies the acoustic signals directly into the external auditory canal. The Bone-Conduction hearing aids can be surgically implanted or worn with a headband and uses vibrotactile stimulation to transmit increased acoustic signals to the cochlea. Cochlear Implants function by circumventing the

normal transduction mechanisms of the outer ear. An electrode is surgically placed into the cochlea and receives input from the external device worn behind the ear.

Unilateral mild-to-moderate hearing loss can be treated with FM systems, bone-conducting hearing aid, cochlear implant, contralateral routing of hearing aids can collect sound from the affected ear and route it to the better hearing ear. Unilateral severe to profound hearing loss have been consistently improved with bone-conduction hearing aids and cochlear implants (75).

Treatment for mild-to-moderate bilateral hearing loss include external devices dedicated to enhancing sound, namely Hearing Aids. Bilateral hearing aid placement is preferred due to the enhanced ability of the wearer to determine sound direction and eliminate background noise(76).

Moderately severe to profound hearing loss can be treated bimodally (a unilateral cochlear implant and a contralateral hearing aid). This approach is useful if simultaneous bilateral surgical insertion of cochlear implants is not feasible, allowing bilateral hearing assistance until the second surgical insertion is possible. Another reason for bimodal hearing aid application is the presence of different levels of hearing in each ear. A bilateral severe or profound hearing loss is best treated with bilateral cochlear implants (77).

Most importantly after fitting of any hearing device either surgically or non-surgically, the patient must receive training by audiologists and speech therapists to help the child adapt to the new method of hearing (78).

CONCLUSION

Children with hearing loss often suffer from anxiety, loneliness, depression, and behavioural problems, aside from cognitive and linguistic deficits. Therefore, it is of great significance to rapidly diagnose and treat children burdened with hearing difficulties. Research has proven that many children with hearing loss cannot be identified solely on recognition of established risk factors. Due to the presence of many unknown genes and the presence of progressive hearing loss, the best way to prevent loss of quality of life is the implementation of routine screening assessments. The advances in rehabilitation and multiple treatment options have been developed to enable hearing-challenged children to attend public schools with their normal hearing peers. Administering targeted interventions before 6 months of age, will allow infants to optimally develop their linguistic abilities.

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REFERENCES:

1. Butcher E, Dezateux C, Cortina-Borja M, Knowles RL. Prevalence of permanent childhood hearing loss detected at the universal newborn hearing screen: Systematic review and meta-analysis. Mathes T, editor. PLOS ONE. 2019 Jul 11;14(7):e0219600.

2. Korver AMH, Smith RJH, Van Camp G, Schleiss MR, Bitner-Glindzicz MAK, Lustig LR, et al. Congenital hearing loss. Nat Rev Dis Primer. 2017 Jan 12;3(1):1–17.

3. Moeller MP. Early Intervention and Language Development in Children Who Are Deaf and Hard of Hearing. PEDIATRICS. 2000 Sep 1;106(3):e43–e43.

4. Wong CL, Ching TYC, Cupples L, Button L, Leigh G, Marnane V, et al. Psychosocial Development in 5-Year-Old Children With Hearing Loss Using Hearing Aids or Cochlear Implants. Trends Hear. 2017 Dec;21:2331216517710373.

5. Early identification of hearing impairment in infants and young children. Int J Pediatr Otorhinolaryngol. 1993 Aug;27(2):201–2.

6. Wang J, Sung V, Carew P, Burt RA, Liu M, Wang Y, et al. Prevalence of Childhood Hearing Loss and Secular Trends: A Systematic Review and Meta-Analysis. Acad Pediatr. 2019 Jul;19(5):504–14.

7. Alvord LS, Farmer BL. Anatomy and orientation of the human external ear. J Am Acad Audiol. 1997 Dec;8(6):383–90.

8. Hunter A, Frias JL, Gillessen-Kaesbach G, Hughes H, Jones KL, Wilson L. Elements of morphology: Standard terminology for the ear. Am J Med Genet A. 2009;149A(1):40–60.

9. Wolak T, Cieśla K, Lorens A, Kochanek K, Lewandowska M, Rusiniak M, et al. Tonotopic organisation of the auditory cortex in sloping sensorineural hearing loss. Hear Res. 2017 Nov;355:81–96.

10. Young Y-H. Contemporary review of the causes and differential diagnosis of sudden sensorineural hearing loss. Int J Audiol. 2020 Apr;59(4):243–53.

11. Sarmento KMA, Sampaio ALL, Santos TGT, de Oliveira CACP. High-frequency conductive hearing loss as a diagnostic test for incomplete ossicular discontinuity in non-cholesteatomatous chronic suppurative otitis media. PLoS ONE [Internet]. 2017 Dec 21 [cited 2021 Apr 22];12(12). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5739461/

12. Smith RJH, Bale JF, White KR. Sensorineural hearing loss in children. Lancet Lond Engl. 2005 Mar 5;365(9462):879–90.

13. Madden C, Halsted MJ, Hopkin RJ, Choo DI, Benton C, Greinwald JH. Temporal bone abnormalities associated with hearing loss in Waardenburg syndrome. The Laryngoscope. 2003 Nov;113(11):2035–41.

14. McClay JE, Tandy R, Grundfast K, Choi S, Vezina G, Zalzal G, et al. Major and minor temporal bone abnormalities in children with and without congenital sensorineural hearing loss. Arch Otolaryngol Head Neck Surg. 2002 Jun;128(6):664–71.

15. Lieu JEC, Kenna M, Anne S, Davidson L. Hearing Loss in Children: A Review. JAMA. 2020 Dec 1;324(21):2195–205.

16. Cuffe KM, Kang JDY, Dorji T, Bowen VB, Leichliter JS, Torrone E, et al. Identification of US Counties at Elevated Risk for Congenital Syphilis Using Predictive Modeling and a Risk Scoring System. Sex Transm Dis. 2020 May;47(5):290–5.

17. DiStefano MT, Hemphill SE, Oza AM, Siegert RK, Grant AR, Hughes MY, et al. ClinGen expert clinical validity curation of 164 hearing loss gene-disease pairs. Genet Med Off J Am Coll Med Genet. 2019 Oct;21(10):2239–47.

18. Koffler T, Ushakov K, Avraham KB. Genetics of Hearing Loss: Syndromic. Otolaryngol Clin North Am. 2015 Dec;48(6):1041–61.

19. Savige J, Ariani F, Mari F, Bruttini M, Renieri A, Gross O, et al. Expert consensus guidelines for the genetic diagnosis of Alport syndrome. Pediatr Nephrol Berl Ger. 2019 Jul;34(7):1175–89.

20. Shearer AE, Hildebrand MS, Smith RJ. Hereditary Hearing Loss and Deafness Overview. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Mirzaa G, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2021 May 3]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1434/

21. Fowler KB, Boppana SB. Congenital cytomegalovirus infection. Semin Perinatol. 2018 Apr;42(3):149–54.

22. Ficenec SC, Schieffelin JS, Emmett SD. A Review of Hearing Loss Associated with Zika, Ebola, and Lassa Fever. Am J Trop Med Hyg. 2019 Sep;101(3):484–90.

23. Organization WH. Childhood hearing loss: strategies for prevention and care [Internet]. World Health Organization; 2016 [cited 2021 May 4]. Available from: https://apps.who.int/iris/handle/10665/204632

24. Cohen BE, Durstenfeld A, Roehm PC. Viral Causes of Hearing Loss: A Review for Hearing Health Professionals. Trends Hear. 2014 Oct 17;18:2331216514541361.

25. Rodenburg-Vlot MBA, Ruytjens L, Oostenbrink R, Goedegebure A, van der Schroeff MP. Systematic Review: Incidence and Course of Hearing Loss Caused by Bacterial Meningitis: In Search of an Optimal Timed Audiological Follow-up. Otol Neurotol Off Publ Am Otol Soc Am Neurotol Soc Eur Acad Otol Neurotol. 2016 Jan;37(1):1–8.

26. Chen JX, Lindeborg M, Herman SD, Ishai R, Knoll RM, Remenschneider A, et al. Systematic review of hearing loss after traumatic brain injury without associated temporal bone fracture. Am J Otolaryngol. 2018 May 1;39(3):338–44.

27. Nguyen T, Jeyakumar A. Genetic susceptibility to aminoglycoside ototoxicity. Int J Pediatr Otorhinolaryngol. 2019 May 1;120:15–9.

28. Maiolino L, Cocuzza S, Conti A, Licciardello L, Serra A, Gallina S. Autoimmune Ear Disease: Clinical and Diagnostic Relevance in Cogan's Sydrome. Audiol Res. 2017 Feb;7(1):6–9.

29. Paul CR, Moreno MA. Acute Otitis Media. JAMA Pediatr. 2020 Mar 1;174(3):308.

30. Harmes KM, Blackwood RA, Burrows HL, Cooke JM, Harrison RV, Passamani PP. Otitis media: diagnosis and treatment. Am Fam Physician. 2013 Oct 1;88(7):435–40.

31. Minovi A, Dazert S. Diseases of the middle ear in childhood. GMS Curr Top Otorhinolaryngol - Head Neck Surg 13Doc11 ISSN 1865-1011 [Internet]. 2014 [cited 2021 Apr 13]; Available from: http://www.egms.de/en/journals/cto/2014-13/cto000114.shtml

32. Pichichero ME. Pathogen shifts and changing cure rates for otitis media and tonsillopharyngitis. Clin Pediatr (Phila). 2006 Jul;45(6):493–502.

33. Piglansky L, Leibovitz E, Raiz S, Greenberg D, Press J, Leiberman A, et al. Bacteriologic and clinical efficacy of high dose amoxicillin for therapy of acute otitis media in children. Pediatr Infect Dis J. 2003 May;22(5):405–13.

34. Leibovitz E. Acute otitis media in pediatric medicine: current issues in epidemiology, diagnosis, and management. Paediatr Drugs. 2003;5 Suppl 1:1–12.

35. Isaacson G. Otoscopic diagnosis of otitis media. Minerva Pediatr. 2016 Dec;68(6):470–7.

36. Zhou F, Shefer A, Kong Y, Nuorti JP. Trends in acute otitis media-related health care utilization by privately insured young children in the United States, 1997-2004. Pediatrics. 2008 Feb;121(2):253–60.

37. Fortanier AC, Venekamp RP, Boonacker CW, Hak E, Schilder AG, Sanders EA, et al. Pneumococcal conjugate vaccines for preventing acute otitis media in children. Cochrane Database Syst Rev. 2019 May 28;5:CD001480.

38. Chesney J, Black A, Choo D. What is the best practice for acute mastoiditis in children? The Laryngoscope. 2014 May;124(5):1057–8.

39. Glasziou PP, Del Mar CB null, Hayem M, Sanders SL. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev. 2000;(4):CD000219.

40. Suzuki HG, Dewez JE, Nijman RG, Yeung S. Clinical practice guidelines for acute otitis media in children: a systematic review and appraisal of European national guidelines. BMJ Open. 2020 May 1;10(5):e035343.

41. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013 Mar;131(3):e964-999.

42. Coker TR, Chan LS, Newberry SJ, Limbos MA, Suttorp MJ, Shekelle PG, et al. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review. JAMA. 2010 Nov 17;304(19):2161–9.

43. Simon F, Haggard M, Rosenfeld RM, Jia H, Peer S, Calmels M-N, et al. International consensus (ICON) on management of otitis media with effusion in children. Eur Ann Otorhinolaryngol Head Neck Dis. 2018 Feb;135(1S):S33–9.

44. Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, Hackell JM, et al. Clinical Practice Guideline: Otitis Media with Effusion (Update). Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg. 2016 Feb;154(1 Suppl):S1–41.

45. Qureishi A, Lee Y, Belfield K, Birchall JP, Daniel M. Update on otitis media – prevention and treatment. Infect Drug Resist. 2014 Jan 10;7:15–24.

46. Martines F, Bentivegna D, Maira E, Sciacca V, Martines E. Risk factors for otitis media with effusion: Case–control study in Sicilian schoolchildren. Int J Pediatr Otorhinolaryngol. 2011 Jun;75(6):754–9.

47. American Academy of Family Physicians, American Academy of Otolaryngology-Head and Neck Surgery, American Academy of Pediatrics Subcommittee on Otitis Media With Effusion. Otitis media with effusion. Pediatrics. 2004 May;113(5):1412–29.

48. Atkinson H, Wallis S, Coatesworth AP. Otitis media with effusion. Postgrad Med. 2015 Jul 4;127(4):381–5.

49. Handzic J, Radic B, Bagatin T, Savic A, Stambolija V, Nevajda B. Hearing in Children with Otitis Media with Effusion – Clinical Retrospective Study. Coll Antropol. 2012 Dec 27;36(4):1273–7.

50. Paradise JL, Campbell TF, Dollaghan CA, Feldman HM, Bernard BS, Colborn DK, et al. Developmental Outcomes after Early or Delayed Insertion of Tympanostomy Tubes. N Engl J Med. 2005 Aug 11;353(6):576–86.

51. Steele DW, Adam GP, Di M, Halladay CH, Balk EM, Trikalinos TA. Effectiveness of Tympanostomy Tubes for Otitis Media: A Meta-analysis. Pediatrics. 2017 Jun;139(6):e20170125.

52. Lambert E, Roy S. Otitis media and ear tubes. Pediatr Clin North Am. 2013 Aug;60(4):809–26.

53. Matsuda Y, Kurita T, Ueda Y, Ito S, Nakashima T. Effect of tympanic membrane perforation on middle-ear sound transmission. J Laryngol Otol Suppl. 2009;(31):81–9.

54. Acuin J. Chronic suppurative otitis media. BMJ Clin Evid [Internet]. 2007 Feb 1 [cited 2021 Apr 21];2007. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2943814/

55. Wilson SA, Mayo H, Fisher M. Clinical inquiries. Are tympanostomy tubes indicated for recurrent acute otitis media? J Fam Pract. 2003 May;52(5):403–4, 406.

56. Master A, Wilkinson E, Wagner R. Management of Chronic Suppurative Otitis Media and Otosclerosis in Developing Countries. Otolaryngol Clin North Am. 2018 Jun;51(3):593–605.

57. Cutajar J, Nowghani M, Tulsidas-Mahtani B, Hamilton J. The Natural History of Asymptomatic Deep Pars Tensa Retraction. J Int Adv Otol. 2018 Apr;14(1):10–4.

58. Maw AR, Hall AJ, Pothier DD, Gregory SP, Steer CD. The Prevalence of Tympanic Membrane and Related Middle Ear Pathology in Children: A Large Longitudinal Cohort Study Followed From Birth to Age Ten. Otol Neurotol. 2011 Oct;32(8):1256–61.

59. Parkes W, Vilchez-Madrigal L, Cushing S, Papsin B, James A. Natural History of Tympanic Membrane Retraction in Children with Cleft Palate. J Int Adv Otol. 2018 Aug;14(2):250–4.

60. Blaney SP, Tierney P, Bowdler DA. The surgical management of the pars tensa retraction pocket in the child--results following simple excision and ventilation tube insertion. Int J Pediatr Otorhinolaryngol. 1999 Oct 25;50(2):133–7.

61. Castle JT. Cholesteatoma Pearls: Practical Points and Update. Head Neck Pathol. 2018 Aug 1;12(3):419–29.

62. Michaels L. An epidermoid formation in the developing middle ear: possible source of cholesteatoma. J Otolaryngol. 1986 Jun;15(3):169–74.

63. Semaan MT, Megerian CA. The pathophysiology of cholesteatoma. Otolaryngol Clin North Am. 2006 Dec;39(6):1143–59.

64. Kuo C-L, Shiao A-S, Yung M, Sakagami M, Sudhoff H, Wang C-H, et al. Updates and knowledge gaps in cholesteatoma research. BioMed Res Int. 2015;2015:854024.

65. Walker D, Shinners MJ. Congenital Cholesteatoma. Pediatr Ann. 2016 May 1;45(5):e167-170.

66. Visvanathan V, Kubba H, Morrissey MSC. Cholesteatoma surgery in children: 10-year retrospective review. J Laryngol Otol. 2012 May;126(5):450–3.

67. Osborn AJ, Papsin BC, James AL. Clinical indications for canal wall-down mastoidectomy in a pediatric population. Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg. 2012 Aug;147(2):316–22.

68. Sahli AS. Developments of children with hearing loss according to the age of diagnosis, amplification, and training in the early childhood period. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg. 2019 Sep;276(9):2457–63.

69. Cebulla M, Ehrmann-Müller D, Shehata-Dieler W. [Objective audiometry and clinical application]. HNO. 2018 Jan;66(1):75–86.

70. Davies RA. Audiometry and other hearing tests. Handb Clin Neurol. 2016;137:157–76.

71. Hall V, Brosch S, Hoffmann TK. [Evaluation of Universal Newborn Hearing Screening and follow-up]. Laryngorhinootologie. 2020 May;99(5):299–307.

72. Musiba Z. Classification of audiograms in the prevention of noise-induced hearing loss: A clinical perspective. South Afr J Commun Disord Suid-Afr Tydskr Vir Kommun. 2020 Mar 3;67(2):e1–5.

73. Gifford KA, Holmes MG, Bernstein HH. Hearing loss in children. Pediatr Rev. 2009 Jun;30(6):207–15; quiz 216.

74. Grundfast KM, Liu SW. What Otolaryngologists Need to Know About Hearing Aids. JAMA Otolaryngol-- Head Neck Surg. 2017 Feb 1;143(2):109–10.

75. Hol MKS, Kunst SJW, Snik AFM, Bosman AJ, Mylanus EAM, Cremers CWRJ. Bone-anchored hearing aids in patients with acquired and congenital unilateral inner ear deafness (Baha CROS): clinical evaluation of 56 cases. Ann Otol Rhinol Laryngol. 2010 Jul;119(7):447–54.

76. Davidson LS, Geers AE, Uchanski RM, Firszt JB. Effects of Early Acoustic Hearing on Speech Perception and Language for Pediatric Cochlear Implant Recipients. J Speech Lang Hear Res JSLHR. 2019 Sep;62(9):3620–37.

77. Litovsky RY, Gordon K. Bilateral cochlear implants in children: Effects of auditory experience and deprivation on auditory perception. Hear Res. 2016 Aug 1;338:76–87.

78. Antia SD, Jones PB, Reed S, Kreimeyer KH. Academic Status and Progress of Deaf and Hard-of-Hearing Students in General Education Classrooms. J Deaf Stud Deaf Educ. 2009 Jul 1;14(3):293–311.

BIOGRAPHY

Sharnu Hendri Snijman grew up in a small town called George, in a scenic part of South Africa known as the Garden Route. He wanted to study medicine since he was little. However, during his High School Finals, he was involved a terrible motorcycle accident. After which he suffered a stroke caused by an aneurysm in his left internal carotid artery. Following successful stent placement during surgery, Sharnu was still determined on pursuing medicine. Unfortunately, he could not qualify to study medicine in his home country after writing his finals in the hospital. Luckily after finishing a BSc Degree in Physiology and Anatomy, he was accepted into Zagreb Medical University to pursue his dream.