

Comorbidities and Conductive Hearing Loss

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ABSTRACT

Hearing loss affects 1.5 billion people worldwide. Conductive hearing loss (CHL) refers to tympanic membrane (ear drum) or ossicle (ear bone) defects as opposed to signals with the nerves or the brain's interpretation. This study will aim to discuss the comorbidities aligned with CHL including Osteogenesis imperfecta (OI), Diabetes Mellitus (DM), Dementia, chromosomal disorders and hormonal disorders as well as the mechanisms linking them to CHL. Mechanisms of CHL include disruption of blood supply, inadequate glucose, distance of joint length and a reduction in collagen synthesis in diabetes. Inadequate removal of mesenchyme in the tympanic cavity in thyroid hormone deficiency. Abnormal bone metabolism in Turner syndrome. Processing of type 1 collagen in Osteogenesis imperfecta and shared neuropathology in dementia. Follow up studies are needed with larger populations to clarify the role these mechanisms play in these diseases and how much they contribute to CHL.

Introduction

Hearing loss affects 1.5 billion people worldwide. Hearing loss can be conductive, sensorineural, or mixed. This study focusses on conductive hearing loss which has a prevalence of 8% in the UK as estimated in 2016 [1].

Conductive hearing loss (CHL) refers to tympanic membrane (ear drum) or ossicle (ear bone) defects as opposed to signals with the nerves or the brain's interpretation. In a number of mammals such as mice, the middle ear is not functional at birth and matures postnatally [2]. This could limit the onset of hearing [3,4].

The ossicles originate from mesenchymal condensations in the early embryo and initially form as cartilage [5]. In mice, the ossicles ossify postnatal while surrounding mesenchyme in the area is cleared and replaced by air before hearing onset at 2 weeks of age [6-9].

Otitis Media (OM) is a leading cause of CHL at school age [10]. Single studies have found CHL in 8% of schoolchildren in Iran whilst a global systematic review found ranges from 0.4% to 64.5% in new-borns [11,12]. Ear drum perforation alone can cause CHL, and documented prevalence ranges have included 1.3% in China, 2.1% in the USA and 3% in South Africa [13-15]. This study will aim to discuss the comorbidities aligned with CHL including Osteogenesis imperfecta (OI), Diabetes Mellitus (DM), Dementia, chromosomal disorders, and hormonal disorders as well as the mechanisms linking them to CHL.

Comorbidities

Osteogenesis Imperfecta

Earlier studies have proved that CHL is most common in younger individuals with Osteogenesis imperfecta (OI) [16,17]. In addition, Otavio et al, found adolescents presented with 30% CHL, versus adults who presented with 21% mixed type hearing loss, in a cross-sectional observational patient study with OI in a hospital in Brazil. In their total sample population conductive hearing loss was the most prevalent among the diverse types of hearing loss. This agrees with others, while disagreeing with others [18-21]. Overall, the pathophysiological mechanism of CHL caused by OI is through defects in the processing of Type I collagen. Mutations involving genes responsible for the synthesis or intracellular processing of type I collagen (COL1) or type II collagen (COL2) is associated with OI.

Disordered type I collagen in the ear targets the auditory structures, leading to early onset hearing loss. There is also a link with OI and ossicle abnormalities.

Berger et al. studied the histopathologic data from eight temporal bones of five patients with type III OI. Evidence of both missing and disordered ossification was found. In another study stapedial crura were thin, deformed and fractured in three OI cases (Type III) [22]. Scanning electron microscope examination of patient's middle ears with OI using the Calcium/Phosphate ratio as a criterion based on characteristic X-ray fluorescence demonstrated that the stapes had a higher ratio of calcium to phosphate and inadequate mineralisation in the OI patient.

compared to normal, 2.6:1 to 2.1, respectively. This finding suggested a change in bone acidification [23].

Metabolic Syndromes

Diabetes Mellitus (DM)

Diabetes mellitus (DM) may affect middle ear function through structural and immunological input. A study by Shimura et al, 2024, on histopathology in the middle areas of Type II diabetic patients demonstrated marked ossicular joint changes. Additionally, a Mendelian randomization study by Kui et al, 2024, demonstrated a causal association between Type 2 DM and a heightened risk of acute suppurative otitis media (ASOM), indicating individuals with DM increased susceptibility to infections of the middle ear due to immune system disturbances [24].

A potential middle ear pathology related to DM is otosclerosis. Otosclerosis is a bone remodelling condition that affects the ossicles (stapes), leading to individuals with otosclerosis experiencing CHL due to the joining of the stapes in the oval window [25]. Studies have suggested a potential link between the two, due to the metabolic and vascular changes because of diabetes that compromise bone homeostasis. Furthermore, hyperglycaemia, a hallmark of DM, disrupts small blood vessels throughout the body. Middle ear structures rely on this blood supply. This may demonstrate that hyperglycaemia-related microangiopathy may affect vascularization of the middle ear and function [26].

Otosclerosis is also linked to female hormones being pro-inflammatory [and the inflammation is linked to elevated bone turnover, during pregnancy the oestrogen elevation causes the start of otosclerosis [27, 28]. This (harmful) oestrogen effect coincides with other studies, where most subjects affected by otosclerosis were female [29, 30]. Recent studies have shown that female hormones increase collagen fibre, the concentration making the female ligaments comparably elastic in relation to males [31, 32]. The increased elasticity in females with otosclerosis, coincides with smaller air bone gap—the difference between air conduction and bone conduction audiometric threshold and better auditory thresholds. Female hormones effect on the ligament elasticity improving the ossicular chain movements [33-36]. During menopause there is also an increase in hearing loss coincident with the protective effect of hormones [37].

In a number of studies tympanometry was used to measure the compliance of the middle ear in diabetic animal models. B tympanograms were higher among the DM type I group and Type A tympanograms which indicate normal ear function were higher among the control groups. Type B tympanogram may indicate fluid in the ear and no movement in the ear drum. The DM type I group type B tympanograms in one study displayed significantly lower amplitudes in comparison to an age matched control [38, 39].

Other studies also reported a decreased compliance in the right ear of type I DM rats versus controls after tympanometry measurements. Explanations to the reduced compliance of include: 1) weakness of elastin and collagen fibres in the tympanic membrane 2) middle ear inflammation; 3) disorders of

the ossicles [40]. In one study hearing impairments in DM type II were associated with diabetic neuropathy [41]. On the other hand, other studies reported increased compliance in the left ear of DM type I rats with tympanometry [42]. This state was seen in children with recurrent acute OM [43]. In contrast this reversed in Type II animals [42]. Explanations for the differences include lesser severity of type II DM [41]. On the other hand, others have concluded that type II DM is more severe in terms of hearing loss at high frequencies. The severe effect is linked. With lower serum levels of protein oxidation products, nitric oxide, and antioxidants [44].

Dementia- Alzheimer's Diseases (AD)

A retrospective cohort study with propensity score matching for patients with and without hearing loss revealed 2.74% of the patients with CHL developed dementia compared to 1.22% of those patients without hearing loss [45]. Another study used two-sample Mendelian randomisation analysis to examine the causal effects of hearing impairment different subtypes and dementia subtypes noted a casual effect of CHL coincided with increased risks of AD [46]. Mechanisms underlying these produced mixed results. An animal study found that CHL by chronic perforation of the tympanic membrane worsens memory loss and reduces glucose metabolism in the hippocampus of mice with AD [47]. Similarly research links CHL and SHL in the ethology of hippocampal neurodegeneration [48, 49]. Additionally, patients with AD demonstrated increased pronounced difficulties in interpreted acoustically degraded speech compared to other types of Dementia [50]. Another study guessed primary progressive aphasia may involve an increased number of central auditory pathways, which may show increased susceptibility to the effects of abnormal folded proteins such as tau proteins among others [51].

The link between hearing loss and dementia could be based on a model proposed by Wayne et al, that discusses an interaction between bottom-up and top-down processing in the brain, and these connect to create the perceptual difficulties in perception, difficulties in cognitive resources, negative psychosocial outcomes, and, impaired cognition [52].

Another study (n=59,675) using a screening service by the Korean National Health Insurance Service to calculate odds ratios (OR) for cognitive impairment according to type of hearing loss subtype. In this study cognitive impairment was significantly associated with CHL (Odds ratio: 1.45, Confidence level 95% 1.20-1.77) [53].

Chromosomal Syndromes

Down Syndrome (DS)

CHL and SHL is present in children with Down syndrome (DS). Earlier studies note otologic and audiological results in children with DS [54, 55]. Children with the hearing loss presented with narrow ear canals, hypotonia of the Eustachian tubes which could lead to OM with effusion as well as loss of hearing.

In one study using the Audiological and Genetic Database (AudGenDB), audiograms of children with Down syndrome were analysed retrospectively for characteristics of hearing loss. This study reported an 11.4% of CHL among the down syndrome patients (Kreicher et al, 2018). In this study a review of CT or MRI scans of temporal bones were taken from 46 patients (92

ears). Clinical indications for radiologic scans included hearing loss, otorrhea, and chronic OM. Sixty-six / 92 ears (71.7%) presented with one abnormality. Ossicular abnormalities were found in seven ears, including anteriorly displacement incus long process, defects in malleus-incus articulation, small ossicles, and bony erosion. This aligns with another study [56].

In another study that looked at Retrospective analysis of temporal bone histopathology of down syndrome patients the incudo stapedial joint of patients with DS was significantly wider than the normal control. In this study 38 to 78% Down's syndrome patients (Trisomy 21) had CHL [57]. This coincides with other studies [58]. The function of this joint is to transfer vibrations between these two ossicles. This joint may be affected by hypotonia and ligament laxity. Other factors contributing to this include otitis media, chronic effusion, eustachian tube dysfunction [60,61]. Other deformities included lowered cartilage density in the eustachian tube small and stenotic ear canals also lead to increased cerumen impaction hindering examination of the area [60].

Turner Syndrome

Turner Syndrome (TS) is a chromosomal abnormality which is caused by partial or complete loss of the X chromosome. Turner syndrome (TS) a symptom of which is ovarian hypoplasia, and this can affect estrogenic production, which has a protective effect on hearing [62]. In addition, a few genes on the short arm of chromosome X may have a regulate hearing function, and their removal may cause abnormal craniofacial abnormalities including auricle abnormalities during development, which may coincide to a prolonged cell cycle [63,64]. Some patients with TS present with abnormalities of the eustachian tube, repeated occurrence of otitis media, middle ear effusion, and cholesteatoma which can lead to middle ear damage and progressive hearing loss [62-65].

Previous studies have identified osteoporosis a disease characterised with low bone mineral density can lead to HL, which may be connected with abnormal bone metabolism in the temporal bone, including bone mass loss in the ossicular chain [66-69]. Yueniwati et al, found that BMD of cochlea, ossicles among other long bones was negatively related with hearing level, indicating that abnormal bone metabolism in TS may link to HL [70].

Hormonal Disorders

Hypothyroidism

The effects of hypothyroidism on auditory development have been demonstrated in several rodent models [71-75]. Middle ear defects can include ossicular abnormalities and defects in cavitation of the middle ear. Most of these abnormalities can be reduced with treatment with thyroxine during hearing maturity although the sensitivity period to hormone is temporary [72,76, 77].

One study looked at severe hypothyroidism in two genetic models and links to hearing abnormalities [78]. DF/B-Prop1df/df (p.S83P) and DW/J-Pou1f1dw/dw (p.W251C) mice have loss of-function mutations in two transcription factors that produce an arrested pituitary cell specification early in development and cannot synthesis thyroid be stimulating hormone, growth hormone, and prolactin. This resulted in a number of defects in the development of the middle ear.

These mutants had persistent mesenchyme at 3 weeks, coinciding

with higher hearing thresholds and the mesenchyme persisted through 4 months in Pou1f1dw/dw mutants, consistent with earlier studies with this mutant [78,79]. In contrast, the mesenchyme was completely gone by 4 months in Prop1df/df mutants, coinciding with their obtainment of normal hearing by that time [80]. Long lasting mesenchyme is linked to middle ear infections, which can influence cognitive functions. There was no difference in otitis media in hypothyroid mice that are susceptible or resistant to hearing loss.

Middle ear abnormalities are noted in Snell dwarf mice, which have pituitary hormone deficiency as well and in hypophysectomised rats [81]. In addition, CHL has been observed in human thyroid diseases [82].

The developmental delay in bone maturation in Pou1f1dw/dw mutants also extended to other areas like the auditory bullae, in which the tympanic ring failed to appear. It was concluded that CHL contributes to the developmental delay in hearing acquisition of Prop1df/df mutants and to the persistent, profound deafness in Pou1f1dw/dw mutants [83].

These findings coincide with outcomes in thyroid stimulating hormone receptor mutant mice (Tshr^{-/-}) and thyroid hormone receptor-deficient mice that are doubly mutant for both receptors (Thra1^{-/-}, Thrab^{-/-}). Both exhibit defects in inner ear and middle ear development including persistent retention of mesenchyme surrounding the ossicles, as well as enlargement of the ossicles and delayed ossification [84, 85].

Growth Hormone Deficiency (GHD)

In one study looking at audiograms of children with GHD, out of 293 ears 47 displayed conductive hearing loss. There was also a seasonal distribution of OM-related conductive hearing loss in children with GHD [86]. Research has described an association between hearing loss and IGF-1, a downstream factor of GH [87-89]. Postnatally, IGF-1 depends on GH release for normal bone and organ development and is important for aspects of ear development including otic neuron proliferation and survival [87-92].

Discussion

OI

The main causes of CHL in OI included ossicular chain immobility as well as discontinuation of the ossicles [16,20, 21,93,94].

Conductive hearing loss was one of the biggest impairments of OI. This agrees with other studies [18,19,95]. While in opposition to others [17,20,21]. Type of OI was also associated with type of hearing loss where Type III OI was linked to CHL [95].

Many patients develop CHL in the second and fourth decade of life and then later this becomes more mixed or sensorineural. A number of authors agree with this [16,20,94-97]. Whilst some studies disagree. Of importance is to check hearing in patients with OI from childhood, so possible social losses decrease.

Strengths of the studies reviewed included big sample sizes. Limitations included differing definitions among the studies for deafness level. Future studies could look at why some decades are more prone than others to CHL and genetic links.

Diabetes

The use of tympanometry measurements in DM participants needs to be combined with more functional and histology tests to get a complete picture. However, this does provide a useful technique for measuring middle ear function in different animal models. Recent evidence suggests alterations in microbiome, that in the nose, ear and oral regions could play a role in the etiology of OI. Given DM is associated with changes in microbiome [98]. Future studies could explore the link between microbiome and DM [99]. De Melker also found that certain measurements can be used to identify middle ear pathologies compared to others. For example, Pneumatic otoscopy is a more sensitive measure for pathologies compared to pure tone audiometry [99].

In terms of structural change of the ossicles in DM type II, one study demonstrated a marked reduction of the joint distance of the include malleal joint in DM patients under 55 years old along with an elongation of the cartilage structure distance in compared to the control group [100]. This may indicate a connection of DM with age related changes. Another study reported that in cases of presbycusis, the joint disc distance and the bone-line distance were longer markedly compared to control cases [101]. Similar cartilage decay and changes in joint integrity is also supported in other studies [102].

An explanation for this includes the sensitivity of chondrocytes for glucose in cartilage [103]. This will impact their ability to maintain normal functions. In patients with DM and osteoarthritis this sensitivity to glucose links to the increase in free radicals [104-106]. A reduction in collagen synthesis and increase in proteolytic enzymes which will affect the structural integrity of cartilage [106]. Distribution of blood supply to the ossicles is also different in DM and ischemic lesions can develop which could affect these [107].

A research gap remains in those studies linking middle ear pathologies with DM. Very few studies exist and further longitudinal studies are needed to elucidate the relationship between DM types I and II and CHL and to explore existing pathophysiology [108, 109]. Studies would need to have larger sample sizes and much higher evidence levels.

Dementia

The increase in hearing loss among dementia patients has been linked to shared neuropathology, cognitive overload, and the social isolation effects. Computational limitations exist in some of the studies surveyed compared to the smaller studies. Database issues including representation from 40% of US patents in some studies. Medical codes inputted could also have introduced variability and therefore bias. Medical codes entered for CHL in some studies may not be reliable owing to the complex nature of CHL. Biomarkers, imaging and clinical diagnoses may be a required for a more correct prediction. Ensuring suitable control groups would also be needed for future studies [45].

Downs Syndrome (DS)

CHL in DS ranges from 75% to 35% [110, 111]. Limitations include study population not a sample of children with DS, but rather a selected group enrolled during care. Second there is limited information on treatments that could have contributed to the outcomes. Study findings indicate the significance of

increasing social awareness about early diagnosis of children with DS who have accompanied hearing issues [112].

Turner Syndrome (TS)

Most TS children are born with a normal hearing level. These children are more likely to develop Middle ear dysfunction early on in age [113].

A number of studies have identified the relationship between karyotype and HL in TS patients [114, 115]. Growth retardation in the skull base due to the absence of SHOX gene and IGF-1 reduction which is essential for the growth of the otic capsule may lead to a growth defect in mastoid, skull base and Eustachian tube which impact middle ear function [116, 117]. Recently, studies have found KDM6A (UTX) gene to be downregulated in TS individuals. This is linked to the immune system and links otitis media and CHL in TS patients [118].

A positive association between these genetic factors and hearing loss in TS patients has not been found in the papers reviewed. Future work could focus on this as well as ensuring there are adequate follow ups for hearing assessment in TS patients where possible.

The studies strengths include large sample sizes and research design. Several limitations exist First; diagnoses were made by codes rather than diagnoses. Second levels of hormones were not present and third, certain biases might affect the results because data regarding risk factors like smoking were not present on the databases used [119].

Growth Hormone Deficiency (GHD)

In vivo and in vitro studies have revealed GHs ability to stimulate the proliferation of cultured outer ear (chondrocytes) of rabbits (Madsen et al, 1983). Increasing the amount of GH increases ossification and this could worsen hearing as seen in acromegaly [120].

However, this is not the case in TS when GH is administered [115, 121]. Interesting middle ear pathology reduces with accelerated bone mineralization of ear cavities in these girls with TS [122].

Children in certain countries like Spain do not receive GH therapy despite being GH-deficient. The reasons are vast: Health agencies may need two negative GH provocative tests, a pituitary MRI, and a specific age. Hence, many children are not treated for GH-deficiency because of these specified requirements.

Although studies in animal models are recent, their results and those in some GH-deficient children show promise with treatment with GH, alone or in combination with other factors. In fact, although GH might not have a direct effect, the hormone induces the expression of several factors, IGF-I, which have positive actions on improving hearing loss [91]. In any case, more studies are needed to analyse in detail the effects that GH can have on a damaged middle ear.

However, there are very few reports that document its efficacy in hearing and this needs to be developed further.

Thyroid Hormone Deficiency

The deafness in Thra+/PV mice can be explained by middle ear issues. The ossicles pass sound waves mechanically between the outer and inner ears. There is amplification of the signal as its transmitted from air which has low impedance to a fluid with high impedance [123]. Remaining mesenchyme would dampen movement of sound between the ossicles.

The ossicles are derived from the first two branchial arches and develop by mesenchymal condensation of mesenchyme. Subsequently, mesenchyme fills the cavity of the middle ear but is later removed to become air filled for low impedance [9, 123]. The mechanism of Mesenchyme clearance is unclear although a number of mechanisms have been speculated including migration, absorption into surrounding structures, or cell death are involved [124]. Thyroid hormone (TH) cooperates with other signals close by to promote mesenchyme clearance. Signals suggested that could play a role in this mesenchyme retention include Treacle nuclear protein. In Tcof1+/- mice carrying mutation of this protein exhibit Treacher-Collins syndrome, a craniofacial disorder with middle ear abnormalities Eya4 could also play a role. In Eya4+/- mice are associated with human deafness DFNA10 [74, 125].

The mesenchyme in the middle ear could also be an origin of bone factors that control growth of the ossicles. These could include bone morphogenetic protein and growth differentiation factor genes as expression of these has been in the mesenchyme.

ME mesenchyme is also composed of factors that control ossicle growth. In the mouse embryo, expression of bone morphogenetic protein and growth differentiation factor genes have been found in mesenchyme [126, 127]. Uncleared mesenchyme in Thra+/PV mice, could have aberrant signalling that will dysregulate ossicle development. Mesenchyme could also play a role in modifying the auditory bulla, the bony covering around the ME cavity [74].

Thyroid Hormone and Ossicular Development

The ossicles in Thra+/PV mice, display a calcification delay and are bigger. This increased size can be explained by the delay that makes a longer window for chondrocyte proliferation in the immature ossicles. Ossicle development and long bone development in these mice are not coupled and further studies are required to understand what signalling factors lie downstream from the thyroid receptor and to what extent they control other signalling factors involved in other bone development such as fibroblast growth factors [128-130].

Craniofacial development disruption is known to produce ossicular abnormalities [5]. Pregnant rats treated with retinoids at gestational day 9 exhibit ossicle hypoplasia [131]. Residual mesenchyme and ossicle disruption was also found in Snell dwarf mice [79]. Pax8-/- mice also show occasional malformation of the stapes with missing crurae [71].

Implications for Middle Ear Disease

THRB mutations which give resistance to thyroid hormone and in which 20 % of patients show some form of hearing loss, mostly conductive is linked to ME defects [132]. This could link the ME disfunction and susceptibility to infections which have been

noted in thyroid disorders [133]. Further studies are needed to look at the causes and links of conductive hearing loss and otitis media that have been mentioned in congenital hypothyroidism.

The middle and inner ear may be targets linked to changes in serum levels of thyroid hormone as determined by in-situ studies [84]. Hypothyroidism and hyperthyroidism may lead to conductive hearing impairment resulting from eustachian tube or linked edema [134].

The ability of thyroxine treatment to improve hearing ability in hypothyroidism remains unclear because the interactions are complex between hormones and their signalling molecules in the middle ear [135-143].

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