UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

PROGRAMA DE PÓS GRADUAÇÃO EM CIÊNCIAS CIRÚRGICAS

COLESTEATOMA ADQUIRIDO DA ORELHA MÉDIA: OBSERVAÇÕES A PROPÓSITO DE 356 PACIENTES

Letícia Petersen Schmidt Rosito

Orientador: Prof. Sady Selaimen da Costa

TESE DE DOUTORADO

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Sumário

INTRODUÇÃO

A primeira descrição do colesteatoma foi feita por Duverney em 1683[1]. " *La carie de l'os arrive quelque fois après ses abcès du conduit, qui s'ouvert derrière l' oreille, et pour lors on a remarqué qu'il s' est fait une fistule au dessus de l'a apohyse mastoide, qui a pénétré dans la sinusotés, et qui a fait tomber en formes d' écailles les petites feuilles qui les composent. Cette carie est accompagnée d'une très mauvaise odeur, et de très fâucheux accidents, et elle pénètre très facilement dans la caísse per le moyen du conduit...ce qui détruisant toutes les parties qui y sont efermées cause une surdité"*. Em seus registros, ele o descreve como uma "cárie" no osso, que aparecia após abscessos na parte posterior da orelha. Essa "cárie" era acompanhada por um odor fétido e "sintomas muito ruins", que "penetrava facilmente no tímpano" e causava surdez. Já o termo colesteatoma foi primeiramente utilizado por Muller em 1838, quando definiu a doença como uma cavidade circundada por pele e preenchida por camadas concêntricas de queratina descamada (debris epiteliais) nas quais cristais de colesterol poderiam ser identificados[2]. Apesar de não ser uma nomenclatura correta, visto que o colesteatoma não contém colesterol (*cole*) e nem gordura (*stea*), o termo ficou consagrado na literatura, mesmo após várias discussões e propostas de outras denominações[3]. Posteriormente, em 1974, Schuknecht descreveu o colesteatoma como acúmulo de queratina esfoliada na orelha média ou outras áreas pneumatizadas do osso temporal, proveniente de epitélio escamoso queratinizado, definição essa amplamente utilizada até os dias atuais[4].

Embora não tenhamos dados epidemiológicos nacionais, o colesteatoma é uma doença pouco frequente, com incidência anual de cerca de 3 por 100.000

crianças e 9,2 por 100.000 adultos caucasianos da Finlândia e Dinamarca[3]. Parece haver uma maior prevalência da doença entre caucasianos, seguidos por afrodescendentes. Um estudo realizado por Kemppainen e colaboradores, em 1999, não encontrou diferença entre a prevalência de colesteatoma entre as diferentes classes socioeconômicas[5].

O caráter destrutivo dessa lesão epitelial determina a erosão das estruturas ósseas adjacentes, podendo levar a várias complicações, algumas graves e potencialmente letais, como meningite, abscesso cerebral e trombose do seio lateral. As complicações mais frequentes, no entanto, são as que resultam da erosão da cadeia ossicular e do comprometimento da orelha interna. A perda auditiva, portanto, é uma característica dessa doença, podendo estar acompanhada de zumbido e/ou vertigem[6].

Cerca de 300 anos se passaram desde a primeira descrição do colesteatoma até a metade do século 20, quando foi alcançado algum consenso a respeito das causas, patogênese e tratamento dessa doença que, na época, tinha uma alta taxa de mortalidade[1]. Mesmo nos dias atuais, há ainda discussões, principalmente quanto à sua patogênese. O adequado entendimento de como realmente se formam e se propagam os colesteatomas implica em um melhor manejo da doença e na possibilidade tratamentos preventivos.

REVISÃO DA LITERATURA

1. Definição e Classificações

Considera-se colesteatoma de orelha média qualquer presença de tecido epitelial esacamoso na fenda auditiva[7]. Embora pouca controvérsia exista a respeito da sua definição, muitas classificações têm sido propostas e discutidas com o decorrer dos anos.

Classicamente, o colesteatoma é classificado em três tipos: 1) Congênito: quando ocorre por detrás de uma membrana timpânica intacta; 2) Adquirido primário: resultante de retrações da membrana timpânica que perdem a sua propriedade de auto limpeza e passam a acumular epitélio; e 3) Adquirido secundário: formado a partir da migração de epitélio através de uma perfuração marginal da membrana timpânica[3,8].

Em 1965, Derlacki e Clemis propuseram uma definição de colesteatoma congênito: além da massa branca perolada medial a uma membrana timpânica intacta, incluía a presença de *pars tensa* e *pars flaccida* normais e ausência de história de otorreia, perfuração da membrana timpânica ou procedimentos otológicos prévios[9]. Contudo, essa concepção tem sido criticada, por ser muito restritiva, pois a existência de um colesteatoma congênito poderia até mesmo provocar a ocorrência de otites médias recorrentes e suas consequências, como a perfuração da membrana timpânica[10].

A classificação do colesteatoma em primário e secundário leva em consideração duas possíveis teorias de formação dos colesteatomas: a da retração e a da migração. Enquanto que a teoria da retração baseia-se na formação do colesteatoma a partir de retrações da membrana timpânica, tanto da

pars tensa quanto da *pars flaccida*, por disfunção crônica da tuba de Eustáquio, a da migração baseia-se na propagação do epitélio escamoso do conduto auditivo externo para a orelha média através de uma preexistente perfuração marginal da membrana timpânica. Apesar dessa classificação ser didática, pode haver controvérsia em alguns casos, pois as membranas timpânicas atelectásicas ou com retrações severas em quadrantes posteriores podem vir a perfurar espontaneamente[11]. Nesses casos, torna-se difícil definir se o colesteatoma se originou a partir da migração de epitélio através da perfuração ou a partir de restos epiteliais que já se encontravam sobre o promontório resultantes da retração.

Existem ainda várias classificações dos colesteatomas baseadas no aspecto otomicroscópico[12], na aparência otoscópica da membrana timpânica[13], na extensão da doença[14] , nos achados cirúrgicos[15] e nos padrões de crescimento típicos dos colesteatomas (ou vias de formação)[16].

Tos propôs, na década de 80, uma classificação baseada na otoscopia: 1) ático, 2) *pars tensa* I(doença marginal) e 3) *pars tensa* II (doença central). Posteriormente, ele apresentou nova classificação baseada no sítio de aparecimento do colesteatoma adquirido, que talvez seja a mais conhecida e utilizada nos dias atuais. Nela, ele divide o colestesteatoma em: 1) atical, definido como retração da *pars flaccida* ou membrana de Sharpnell, que se estende no ático e adito e eventualmente para o antro, mastoide e cavidade timpânica, 2) do seio, retração póstero-superior ou perfuração da *pars tensa* que se extende para o seio timpânico e tímpano posterior, 3) da tensa, retração e adesão de toda a *pars tensa*, envolvendo o orifício timpânico da tuba auditiva[12].

Jackler, em 1989, propôs uma nova classificação, considerando as vias de crescimento típicos dos colesteatomas. Desse modo, além da localização,

também foram considerados a via de formação e o modo de progressão do colesteatoma na orelha média e na mastoide. Ele os dividiu, portanto, segundo a sua ordem de frequência, em epitimpânicos posteriores, mesotimpânicos posteriores e epitimpânicos anteriores e considerava a possibilidade de envolvimento de mais de uma rota[16]. A importância da diferenciação dos colesteatomas segundo seus padrões típicos de crescimento reside no maior entendimento da patogênese da doença e determinação de prognósticos e abordagens terapêuticas muitas vezes distintas. Por englobar os colesteatomas epitimpânicos anteriores, embora raros e por considerar a possibilidade da existência de mais de uma rota de crescimento concomitantemente, a classificação de Jackler é mais abrangente do que a de Tos.

2. Perda auditiva

A ocorrência de perda auditiva em pacientes com otite média crônica está bem estabelecido. A presença de colesteatoma, no entanto, determina um maior impacto auditivo, tanto no aspecto condutivo quanto neurossensorial[17]. Um estudo prévio do nosso grupo, que incluiu apenas crianças e adolescentes com otite média crônica, demonstrou que os tamanhos das diferenças aeroósseas (*gaps*) eram significativamente maiores, em todas as frequências analisadas, nos pacientes com diagnóstico de colesteatoma do que naqueles com perfuração da membrana timpânica[17] .

A perda auditiva condutiva no colesteatoma é atribuída à erosão ossicular, característica da doença. Jeng observou que a erosão da cadeia ossicular era mais frequente em pacientes com otite media crônica com colesteatoma do que naqueles sem ele[18]. Quanto ao envolvimento da cadeia ossicular, em 1979 Tos

relatou que a bigorna foi o ossículo mais frequentemente erosado em pacientes com colesteatoma[19], achado esse corroborado por Maresh e colaboradores[20]. Alterações ossiculares foram observadas por Albera e colaboradores em 82% dos pacientes com colesteatoma, sendo novamente a bigorna o ossículo mais envolvido (78%), seguida pelo estribo (29%) e martelo (20%)[21]. Tos ainda demonstrou que as erosões da cabeça do martelo e do corpo da bigorna foram mais frequentes nos colesteatomas aticais, enquanto que a reabsorção do corpo da bigorna juntamente com a supra estrutura do estribo foram mais comuns nos do seio, e a reabsorção de todos os ossículos foi mais frequente nos da tensa[19]. Jeng e colaboradores, no entanto, não encontraram diferença na erosão ossicular entre colesteatoma atical e de tensa[18]. Maresh e colaboradores verificaram que, nos colesteatomas secundários, o estribo foi mais frequentemente erosado do que nos primários[20]. As diferentes classificações utilizadas nesses estudos, no entanto, tornam difícil a comparação dos resultados.

Os estudos que correlacionam a erosão da cadeia ossicular com o tamanho da perda auditiva são escassos. Silveira Netto não demonstrou diferença significativa no tamanho dos *gaps*, comparando colesteatomas epitimpânicos posteriores e mesotimpânicos posteriores, embora o estudo tenha sido realizado somente em pacientes pediátricos e, por essa razão, talvez o seu número total de pacientes incluídos tenha sido restrito[17]. Já Jeng e colaboradores, na busca por preditores de descontinuidade ossicular em pacientes com otite média crônica, não conseguiu correlacionar o *gap* pré-operatório com as alterações na cadeia ossicular encontradas durante o procedimento cirúrgico[20]. Martins e colaboradores, no entanto, estudando apenas pacientes com colesteatoma, verificaram que o estado de cada ossículo estava significativamente associado

com o *gap* de uma forma gradual e independente, e que essa associação foi maior com a bigorna[22].

A perda sensorineural decorrente da otite media crônica tem sido demonstrada em vários estudos[23- 25]. Em um estudo prévio do nosso grupo, observamos, como o esperado, que pacientes com otite média com colesteatoma apresentavam um maior dano na orelha interna do que aqueles sem colesteatoma. A perda sensorineural no colesteatoma pode ser decorrente de erosão direta de estruturas da orelha média, como as fístulas que mais frequentemente comprometem o canal semicircular lateral[23]. Mediadores inflamatórios ou toxinas bacterianas, por outro lado, presentes na orelha média de pacientes portadores de colesteatoma, podem atravessar a janela redonda e danificar diretamente as células ciliadas da cóclea. Eisenman and Parisier demonstraram que o colesteatoma estava associado a uma diminuição da função coclear, mesmo na ausência de invasão franca da orelha interna pela doença[23]. Na atualidade, no entanto, ainda restam dúvidas se a perda sensorineural pode ser evidenciada tanto em crianças quanto em adultos, se pode ser demonstrada em todos os tipos de colesteatoma, independentemente da sua via de formação, e ainda se há correlação entre o *gap* aeroósseo e o dano observado na orelha interna.

3. Diferenças entre crianças e adultos

Ainda existem controvérsias na literatura se os colesteatomas em crianças são de fato mais agressivos do que os colesteatomas em adultos. Vários estudos demostraram que os índices de recidiva dos colesteatomas pediátricos são 2 a 3

vezes maiores[26-28] e que os colesteatomas em crianças teriam padrões de crescimento mais extensos do que em adultos[29].

Bujia e colaboradores demonstraram uma maior taxa de proliferação celular nos colesteatomas de crianças, definida pelo aumento dos níveis de MIB1, um antígeno antinuclear expresso por células ativas no ciclo celular[30]. Dornelles e colaboradores demonstraram também que os colesteatomas pediátricos apresentaram um grau inflamatório mais exacerbado e produziram mais metaloproteinases do que em adultos, o que poderia corresponder a um maior grau de agressividade da doença[31].

Há, no entanto, uma escassez de estudos que comparem as características clínicas e fisiopatológicas dos colesteatomas, bem como o comprometimento auditivo, tanto condutivo quanto sensorineural, entre as duas classes etárias

4. Patogênese do colesteatoma e o estudo da orelha contralateral

Várias teorias a respeito da patogênese do colesteatoma têm sido propostas. As principais são:

4.1 Teoria congênita

Segundo essa teoria, proposta por Korner e Virchow em 1863, os colesteatomas nasceriam a partir de ninhos de células epiteliais que, ao longo dos anos, se multiplicariam até a formação de um tumor epitelial. Atualmente, acredita-se que alguns raros casos de colesteatoma possam realmente ser congênitos e que sejam originados de restos embrionários[32].

4.2 Teoria da metaplasia

Proposta por von Tröltsch em 1864, essa teoria postula que o epitélio escamoso queratinizado do colesteatoma seja produto da metaplasia da mucosa da orelha média[33]. Sadé deu suporte a essa teoria no momento em que observou que o epitélio pluripotente da orelha média e da mastoide poderia se transformar, quando estimulado pela inflamação, em epitélio escamoso queratinizado metaplásico[34]. A observação de ilhas de epitélio escamoso em biópsias de mucosa de orelha média em pacientes pediátricos com otite média com efusão também corrobora essa teoria[35].

4.3 Teoria da migração

Habermann, em 1888, e Bezold, em 1890, propuseram que o epitélio escamoso do conduto auditivo externo poderia migrar, através de uma perfuração marginal da membrana timpânica, para a orelha média[3]. A migração de epitélio, após a indução de perfuração da membrana timpânica por diversos agentes, tem sido demonstrada em vários modelos animais[3]. Mas, segundo Sudhoff e Tos, clinicamente, é difícil encontrar algum suporte para essa teoria[36]. Eles, por exemplo, nunca observaram uma perfuração aguda da *pars tensa* ou da *pars flaccida* que permitiria a migração de epitélio escamoso através dela[36]. Um trabalho recente do nosso grupo também demonstrou que, além das perfurações marginais serem muito raras, a maioria delas possuía características sugestivas de retração da membrana timpânica moderada ou severa previamente à ocorrência da perfuração[37].

4.4 Teoria da hiperplasia basal

Também chamada de teoria de proliferação papilar, baseia-se no fato de que a infecção pode levar à proliferação de cones epiteliais na camada basal do epitélio escamoso queratinizado da *pars flaccida* ou *pars tensa*[36]. Lange, em 1925, observou que células epiteliais do epitélio escamoso queratinizado da *pars flaccida* poderiam invadir o espaço subepitelial e formar um colesteatoma atical[38] . Posteriormente, outros estudos demonstraram que pseudópodes da camada de células basais parecem quebrar a lâmina basal, permitindo que queratinócitos epidermais invadam a lâmina própria, formando cistos de inclusão e podendo se expandir e formar colesteatomas[35].

4.5 Teoria da retração

Também chamada de teoria da invaginação, foi apresentada em 1933 por Wittmaack[39]. De acordo com ela, a *pars flaccida* ou ocasionalmente a *pars tensa* retrairiam em direção à orelha média[39]. O mecanismo subjacente da formação da bolsa de retração, provavelmente, estaria relacionada com pressão negativa, inflamação ou ambos. A retenção de acúmulo de queratina em bolsas de retração profundas estabeleceriam o diagnóstico de colesteatoma. A perda da propriedade de autolimpeza da bolsa de retração induziria à expansão do epitélio nos espaços da orelha média e mastoide[3].

4.6 Teoria da implantação

Existem ainda dois outros processos de formação dos colesteatomas que devem ser mencionados: a) os colesteatomas iatrogênicos, que surgem após cirurgias prévias da orelha média, como timpanoplastias e timpanotomias para

tubo de ventilação e b) pós-traumáticos, que se originam com a implantação de epitélio escamoso na orelha média durante o processo cicatricial[3,32].

A teoria atualmente mais aceita de patogênese dos colesteatomas adquiridos é a da retração[3]. Experimentos em cobaias conduzidos por Chole e colaboradores demostraram o desenvolvimento de colesteatoma a partir de retração da membrana timpânica. Em seus estudos, observaram que a cauterização da tuba de Eustáquio de gerbils resultou em colesteatoma em 40% a 75% das orelhas após 16 semanas da obstrução[40,41] . Demostraram ainda que a infecção por *Pseudomonas aeruginosa* tornou os colesteatomas mais agressivos e com um crescimento mais rápido, quando comparados com os não infectados[42].

A comprovação da progressão das retrações timpânicas para colesteatoma e a identificação de fatores potencializadores ou agravantes em humanos, contudo, é muito mais difícil. Uma coorte envolvendo 215 pacientes com retrações da membrana timpânica conduzida por Sadé e colaboradores em 1981 observou a ocorrência de colesteatoma em uma orelha com uma grande bolsa de retração em *pars tensa* (2% do total das retrações de *pars tensa*) e em duas orelhas com bolsas de retração moderadas e severas de *pars flaccida* (2% do total das retrações de *pars flaccida*)[11]. O estudo, no entanto, envolveu retrações de vários graus de severidade e com um tempo de seguimento muito variável (de 6 a 94 meses, com uma média de 34 meses)[11]. Sudhoff e Tos, estudando retrações aticais em crianças submetidas à adenoidectomia e à timpanotomia para colocação de tubos de ventilação, observaram a incidência de colesteatomas aticais de 0,2 % 3 a 8 anos após a cirurgia, de 0,6% após 10 a 16 anos e de 1,7% 11 a 18 anos após[43]. O fator limitador dessa coorte foi a grande perda de

seguimento dos pacientes com o decorrer do tempo. Eles iniciam o estudo com um número de 527 orelhas, avaliam 362 no segundo período de observação e terminam o estudo com apenas 214. Na avalição da mesma coorte de crianças em relação à prevalência de patologias de *pars tensa*, a incidência de retrações severas posterosuperiores foi de 3,2 % a 5,1% e, apesar de relatarem que observaram alguns colesteatomas de seio, eles não quantificaram. Cassano e Cassano, em um estudo que incluiu 40 orelhas com retração da membrana timpânica em crianças não submetidas a tratamento por razões diversas, como contraindicações anestésicas ou recusa dos pais, observaram a progressão de retrações severas (graus III e IV de Sadé) para colesteatoma em 20% dos casos após dois anos de seguimento[44].

A análise crítica desses estudos remete à grande dificuldade na realização de coortes bem conduzidas para o entendimento da patogênese dos colesteatomas adquiridos. Além disso, é necessário um tempo de seguimento de vários anos para a observação da progressão das alterações. Se forem incluídos pacientes com orelhas normais ou com retrações leves, no entanto, a incidência de colesteatoma será ainda mais baixa, visto a observação de Sadé de que quanto mais avançada uma retração ou atelectasia, menor a chance dessa se resolver espontaneamente, sendo o contrário também verdadeiro[11].

A perda de pacientes durante o período de estudo resulta ainda em um erro de aferição, o que pode, muitas vezes, invalidar os resultados. As questões éticas também restringem o desenvolvimento de estudos de seguimento. Nos estudos de Sudhoff e Tos, por exemplo, só foram seguidas crianças submetidas previamente à adenoidectomia e à timpanotomia para colocação de tubo de ventilação, o que pode ter contribuído para a baixa incidência de colesteatoma durante o longo

período de acompanhamento[36,43]. Por outro lado, questões éticas inviabilizam a simples observação das otites médias secretoras crônicas e das retrações moderadas e severas que já determinam um comprometimento auditivo significativo[44].

Diante de tantas dificuldades na realização de estudos ideais, há a busca de maneiras alternativas para o entendimento da fisiopatogênese do colesteatoma em humanos. Na teoria do *continuum* para a patogênese da otite média crônica, Paparella e colaboradores postulam que as formas iniciais de otite média (otite média aguda, otite média serosa e, principalmente, otite média secretora) podem, com o passar do tempo e na ausência de mecanismos frenadores, evoluir para cronificação[45]. Da mesma forma, a perpetuação da pressão negativa dentro da orelha média, necessária para o desenvolvimento das retrações timpânicas, depende inicialmente da disfunção da tuba de Eustáquio, mas provavelmente necessita das trocas gasosas através da mucosa inflamada para a sua manutenção[46]. A otite média secretora crônica propicia, portanto, um ambiente inflamatório ideal para o aumento das trocas gasosas através da mucosa da orelha média, perpetuação da pressão negativa e desenvolvimento de retrações timpânicas e, posteriormente, colesteatomas. Como a otite média secretora geralmente é bilateral[47,48], a sua progressão para alterações mais graves deveria, portanto, também ocorrer nas duas orelhas. Partindo desses princípios, nosso grupo vem desenvolvendo, desde 2008, estudos clínicos[49], histopatológicos[50], radiológicos[51] e funcionais[17] da orelha contralateral em pacientes com otite média crônica, todos eles demonstrando uma alta prevalência de alterações. Dessa forma, o estudo da orelha contralateral é uma alternativa mais viável, embora

indireta, para o estudo da patogênese das otites médias crônicas, especialmente as colesteatomatosas.

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OBJETIVOS

1. Determinar a prevalência de colesteatoma em pacientes com otite media supurativa crônica em um hospital universitário terciário e determinar as características desses pacientes e suas lesões;

2. Revisar as classificações dos colesteatomas existentes e propor uma nova e mais abrangente, baseada tanto na videotoscopia quanto na patogênese;

3. Avaliar a perda auditiva em pacientes com colesteatoma e investigar as diferenças entre crianças e adultos;

4. Determinar se o colesteatoma está associado à perda auditiva sensorineural e investigar se a idade do paciente, a via de formação do colesteatoma e o tamanho da diferença dos limiares audiométricos aeroósseos contribuem para essa alteração;

5. Verificar se há diferenças audiométricas entre colesteatomas mesotimpânicos posteriores e epitimpânicos posteriores;

6. Descrever a orelha contralateral de pacientes com colesteatoma e investigar potenciais diferenças de acordo com a idade e suas vias de crescimento;

7. Estudar a orelha contralateral de pacientes com colesteatoma com ênfase nas retrações da membrana timpânica e nos colesteatomas.

Características de 356 pacientes com colesteatoma de orelha média

Clinical description of 356 patients with middle ear cholesteatoma

Letícia Petersen Schmidt Rosito[1], Fábio André Selaimen[2], Yuri Petermann Jung[3], Marcos Guilherme Tibes Pauletti[3], Larissa Petermann Jung[3], Luiza Alexi Freitas[3],
Sady Selaimen da Costa[4]

[1] Otorrinolaringologista no Hospital de Clínicas de Porto Alegre
Mestre em Cirurgia pela Universidade Federal do Rio Grande do Sul

[2] Residente em otorrinolaringologia pelo Hospital de Clínicas de Porto Alegre

[3] Acadêmicos da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul

[4] PhD, Professor do Departamento de Oftalmologia e Otorrinolaringologia da Universidade Federal do Rio Grande do Sul.

Autor para Correspondência:

Letícia Petersen Schmidt Rosito

Rua Ramiro Barcelos, 2350

Serviço de Otorrinolaringologia (Zona 19)

Porto Alegre –RS , Brasil

CEP 90035-903

RESUMO

Introdução: O colesteatoma é uma lesão destrutiva que pode determinar complicações potencialmente letais. Por ser uma doença rara, não existem estudos no Brasil que descrevam as características dos pacientes portadores dessa doença. O presente estudo tem o objetivo de determinar a prevalência e descrever o perfil dos pacientes com colesteatoma de orelha média atendidos em um hospital de referência do sistema público de saúde.

Método: Estudo transversal que incluiu 356 pacientes com colesteatoma após avaliação de 1435 pacientes com otite média crônica, sem tratamento cirúrgico prévio. Foi realizada anamnese detalhada e otoendoscopia, além de revisão de prontuários para busca de dados cirúrgicos.

Resultados: Dos pacientes com otite média crônica, apenas 24,8% foram diagnosticados com colesteatoma. A média de idade foi de 32,77 anos; 53,1% eram do sexo feminino e 63,8% eram adultos. Colesteatoma foi observado bilateralmente em 16,9%. Os epitimpânicos anteriores corresponderam a 2,3%, os epitimpânicos posteriores, 34,3%, os mesotimpânicos posteriores, 33,5%, duas vias, 14,4% e indeterminado,s 15,5%. A prevalência de malformações palatinas foi de 4,3%. Dos pacientes operados, 6,8% foram submetidos à timpanoplastia, 17,7% à timpanomastoidectomia fechada e 75,5% à timpanomastoidectomia aberta.

Conclusão: O colesteatoma foi mais frequente em adultos do que em crianças. A prevalência de colesteatomas mesotimpânicos posteriores e epitimpânicos posteriores foi muito semelhante, e não se observou diferença na frequência de malformações palatinas entre crianças e adultos. Na maioria dos

pacientes submetidos à cirurgia, a timpanomastoidectomia aberta foi o procedimento de escolha.

Palavras-chave: colesteatoma; orelha média; bilateral; classificação; cirurgia

SUMMARY

Introduction: Cholesteatoma is a destructive lesion that can determine potentially lethal complications. Since it's a rare disease, there are few studies in Brazil describing the characteristics of these patients. The present study aims to determine the prevalence and describe the profile of patients with middle ear cholesteatoma treated at a referral hospital in public health system.

Method: Cross-sectional study, including 356 patients with cholesteatoma after evaluation of 1435 patients with chronic otitis media without prior surgical treatment. Otoendoscopy and detailed clinical history were performed, in addition to revision on files of surgical data.

Results: From patients with chronic otitis media, only 24.8 % were diagnosed with cholesteatoma. The average age was 32.77 years old, 53.1 % were female and 63.8 % were adults. Cholesteatoma was observed in both ears in 16.9 %. Anterior epitympanic was 2.3%, posterior epitimpanic was 34.3 %, mesotympanic was 33.5 %, two-way cholesteatoma was 14.4 %, and undetermined was 15.5 %. The prevalence of cleft malformations was 4.3%. From patients who underwent surgery, in 6.8 % was performed tympanoplasty, in 17.7% closed tympanomastoidectomy and 75.5 % to open tympanomastoidectomy.

Conclusion: The cholesteatoma was more frequent in adults than in children. The prevalence of mesotympanic cholesteatoma and posterior epitimpanic was very similar and no difference in the frequency of palatal defects in

children and adults was observed. In most patients who were undergone surgery, open tympanomastoidectomy was the procedure of choice.

Key Words: cholesteatoma; middle ear; bilateral; classification; surgery

Introdução

O colesteatoma é considerado uma lesão epitelial benigna, de expansão gradual e destrutiva, que acomete a fenda auditiva e estruturas adjacentes[1]. O acúmulo epitelial e a erosão óssea, características da doença, tipicamente resultam em otorreia contínua e hipoacusia. Com a progressão do colesteatoma, pode haver também o comprometimento da orelha interna[2,3] e do nervo facial, além de complicações graves, como meningite e abscesso cerebral[4].

A sua incidência estimada na população em geral é de 3,7 a 13,9/ 100.000[5,6]. Essa incidência é menor em crianças (3/100.000) do que em adultos (9/100.000)[7]. Por ser uma doença pouco frequente, estudos epidemiológicos a seu respeito, especialmente no nosso país, são escassos. Essa falta de dados impossibilita a comparação de estudos realizados no Brasil com os demais, visto que não sabemos se realmente tratam-se de populações semelhantes.

Os objetivos deste estudo são determinar a prevalência de colesteatoma em pacientes com otite média crônica (OMC); descrever o perfil dos pacientes com OMC colesteatomatosa; e verificar as técnicas cirúrgicas mais utilizadas em um hospital de referência do sistema público de saúde.

Método

O delineamento deste estudo foi do tipo transversal, incluindo 1435 pacientes consecutivos com OMC, atendidos durante o período de agosto de 2000 a março de 2013, no Ambulatório de Otite Média Crônica do Hospital de Clínicas de Porto Alegre.

O critério de inclusão foi o diagnóstico de OMC com colesteatoma após análise das videotoscopias. Os critérios de exclusão foram: recusa em participar do estudo, história de qualquer cirurgia otológica prévia, com exceção de timpanotomia para colocação de tubo de ventilação e impossibilidade de limpeza adequada das orelhas e/ou de videotoscopia para documentação apropriada.

No momento da primeira avaliação, foi realizada uma anamnese detalhada e dirigida, bem como exame otorrinolaringológico completo. Após limpeza cuidadosa das orelhas, foi realizada videotoscopia com fibra ótica de zero grau e 4 mm (Karl Stortz). Ambas as orelhas foram registradas sequencialmente, utilizando o software Cyberlink Powerdirector (versão 7, 2008). Após a anamnese e exame físico, os pacientes foram submetidos à audiometria tonal, com o uso do audiômetro *Interacoustic* AD 27 com fones supraurais TDH-39, para a determinação dos limiares de via aérea, via óssea e o *gap* aeroósseo. O *gap* foi calculado através da diferença entre a via aérea e a via óssea. Mascaramento com ruído de banda larga foi utilizado quando necessário. Nas crianças pequenas foi realizada audiometria condicionada lúdica com fones supraurais. Quando necessário, a audiometria era concluída após duas sessões para a confirmação dos limiares obtidos. A via aérea, via óssea e o *gap* foram descritos através da média tritonal, calculada pela média dos limiares em 500, 1000 e 2000 Hz, que representam a área de reconhecimento de fala.

As videotoscopias registradas foram independentemente revisadas durante uma reunião clínica. Para a avaliação das imagens, foram utilizados protocolos específicos de maneira sistemática, de acordo com as definições descritas a seguir pelo pesquisador sênior.

Os colesteatomas foram então classificados, de acordo com classificação modificada de Jackler[8], segundo a sua via de formação em:

1. Epitimpânico anterior: quando originado anteriormente à cabeça do martelo.
2. Epitimpânico posterior: quando originado exclusivamente na *pars flaccida.*
3. Mesotimpânico posterior: quando originado exclusivamente no quadrante posterosuperior da *pars tensa.*
4. Epi e mesotimpânico posterior ou duas vias: quando proveniente tanto da *pars flaccida* quando da *pars tensa*.
5. Indeterminado: quando a via de formação do colesteatoma não pode ser determinada pela imagem de videotoscopia.

Foram considerados crianças os pacientes com idade abaixo de 18 anos, segundo os critérios da Organização Mundial de Saúde.

Os prontuários bem como as descrições cirúrgicas dos pacientes que já haviam sido operados foram revisados.

O Grupo de Pesquisa e Pós Graduação da nossa instituição aprovou o projeto em seus aspectos éticos e científicos. Todos os pacientes incluídos nos estudos assinaram previamente um consentimento informado, autorizando o uso de seus dados de forma anônima neste estudo científico.

Os dados foram tabulados e analisados através do programa SPSS Statistics Software (version 20). A análise estatística foi feita com os testes de Mann Whitney para a verificação de diferença entre os tempos de duração da doença e com o teste Exato de Fisher para a diferença de prevalência de

malformações palatinas entre crianças e adultos, considerando-se estatisticamente significativos os valores de *p* menores que 0,05.

Resultados

Dos 1435 pacientes com OMC avaliados no estudo, observou-se a presença de colesteatoma em apenas 356 (24,8%). A média de idade dos pacientes selecionados foi de 32,77, desvio padrão (dp) ±19,93 (2-82 anos) e 189 (53,1%) eram do sexo feminino. Adultos corresponderam a 63,8% da população estudada.

O colesteatoma foi identificado na orelha direita em 195 pacientes (54,8%). Na avaliação da orelha contralateral, apenas 123 delas (34,6%) eram normais, e em 60 (16,9%) foi identificado colesteatoma. A prevalência das diferentes vias de formação dos colesteatomas na nossa população está demonstrada na figura 1.

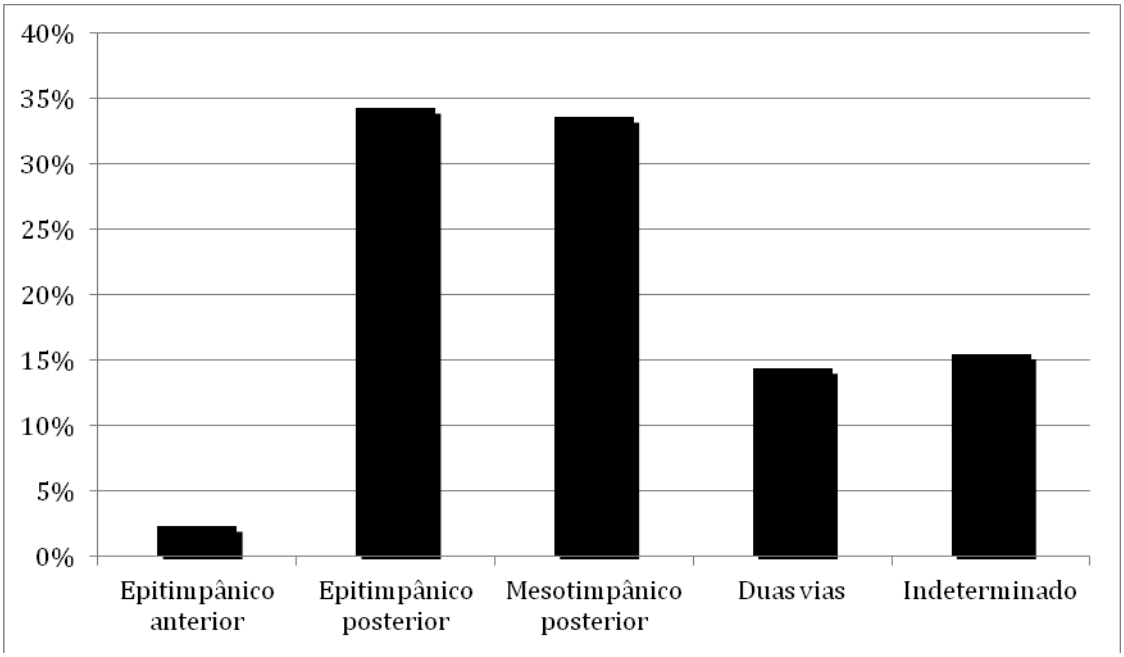

Figura 1: *Prevalência dos colesteatomas segundo a sua via de formação.*

As principais queixas dos pacientes no momento da primeira avaliação no nosso serviço estão demonstradas na figura 2. Hipoacusia, associada ou não à otorreia, foi a queixa principal de 84,4% da população estudada, e foi observada otorreia em 87% .

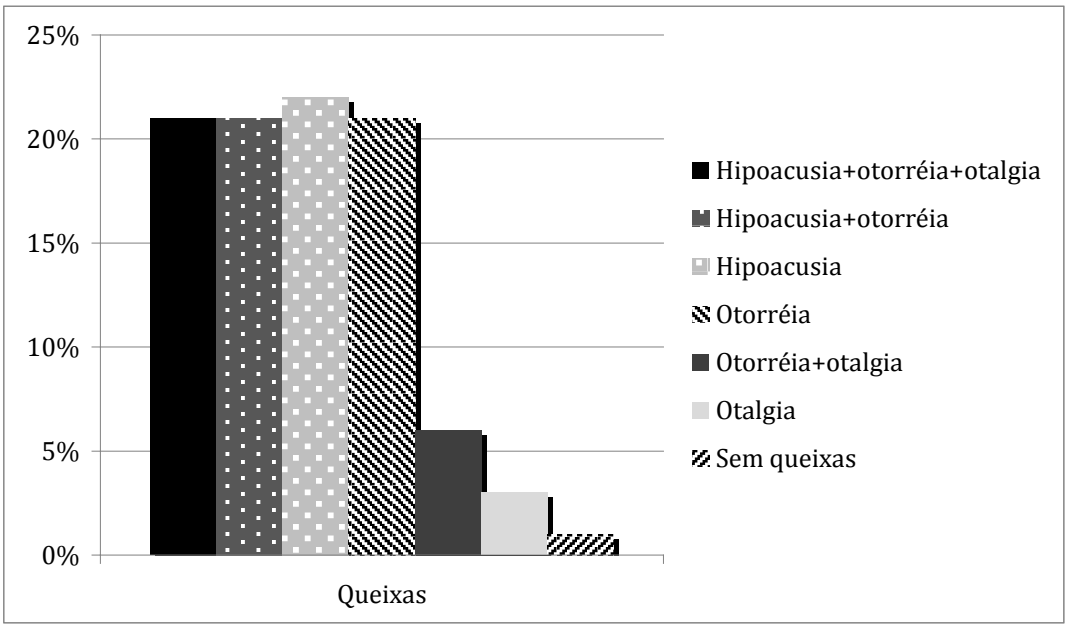

Figura 2: *Frequência das principais queixas dos pacientes com colesteatoma no momento da primeira avaliação.*

A média de tempo do início dos sintomas até nossa avaliação foi de 13,52 anos (dp± 13,72, variando de 0,4 a 70 anos). Nas crianças, essa média foi de 6,79 anos e mediana de 6 anos, sendo nos adultos de 17,34 anos e de 13, respectivamente. Houve diferença estatisticamente significativa entre os grupos (p<0,001).

A prevalência de malformações de palato na nossa população foi de 4,3%. Não foi observada diferença significativa na prevalência de malformações palatinas, quando comparados crianças e adultos (p=0,59), conforme demonstrado na figura 3.

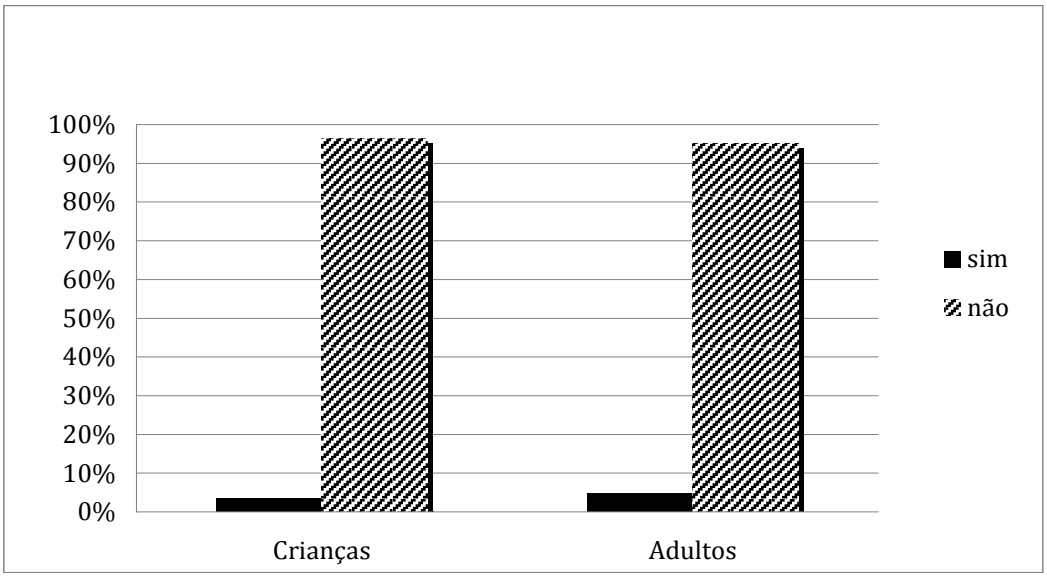

Figura 3: *Comparação das prevalências de malformações palatinas entre crianças e adultos.*

Dos pacientes avaliados, 329 (92,41%) realizaram audiometria. Quanto aos limiares de via óssea e de via aérea, a média tritonal foi 17,08± 16,16 dB e 46,35±22,34 dB, respectivamente. Quanto ao tamanho dos *gaps*, a média tritonal foi de 29,84± 13,61. A prevalência do tamanho dos *gaps* (média tritonal) na nossa população está demonstrada na figura 4.

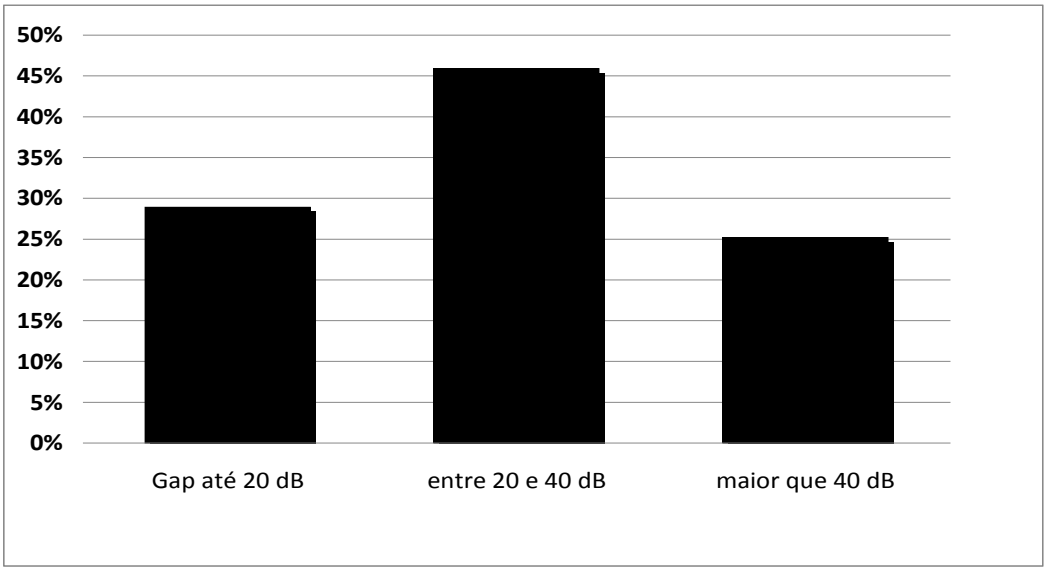

Figura 4: *Prevalência dos tamanhos das diferenças aeroósseas na média tritonal*

Dos pacientes avaliados, 146 (46,1%), ainda não haviam realizado cirurgia no momento do estudo ou haviam perdido acompanhamento. Dos pacientes que realizaram cirurgia, 13 (6,8%) foram submetidos à timpanoplastia, 34 (17,7%) à timpanomastoidectomia fechada e 145 (75,5%) à timpanomastoidectomia aberta.

Discussão

O colesteatoma, apesar de ser uma doença agressiva associada a graves complicações, é pouco prevalente. O nosso estudo, realizado em um centro de referência estadual da doença, incluiu 356 pacientes (416 orelhas) com colesteatoma ao longo de 10 anos. A prevalência de colesteatoma dentre os pacientes com OMC e sem tratamento cirúrgico prévio foi de 24,8%.

Embora existam muitos estudos a respeito do colesteatoma, poucos são descritivos e interessados nas características dos pacientes acometidos por essa doença. No presente estudo, nós observamos uma prevalência maior de adultos do que crianças (68,8% e 36,2%, respectivamente), o que corrobora trabalhos anteriores que demonstraram que a incidência de colesteatoma é maior em adultos[7]. A hipoacusia e a otorreia foram as queixas principais da maioria dos pacientes, e 87% deles apresentavam otorreia no momento da avaliação. A queixa de hipoacusia foi confirmada pela audiometria que demonstrou que a grande maioria dos pacientes apresentava perda auditiva condutiva com gaps aeroósseos maiores de 20 dB na área de reconhecimento de fala.

A prevalência de bilateralidade do colesteatoma em nossa casuística foi de 16,9%, similar a estudos prévios[9]. Colesteatomas epitimpânicos posteriores e mesotimpânicos posteriores foram observados com igual frequência na nossa população, o que contraria a maioria dos estudos que apontam o colesteatoma

atical como o mais prevalente [8,10]. Além disso, observamos também a ocorrência de colesteatomas epitimpânicos anteriores, esses muito raros, e de colestetomas que se desenvolveram envolvendo tanto a *pars tensa* como a *pars flaccida*, concomitantemente, que nós denominamos duas vias e que corresponderam a 15% dos casos. Em cerca de 15% dos pacientes não foi possível determinar com precisão a via de formação dos colesteatomas, sendo, portanto, classificados como indeterminados.

A grande média de tempo entre o aparecimento dos sintomas e a primeira avaliação no nosso serviço demonstra as dificuldades de acesso dos pacientes com colesteatoma ao atendimento público no nosso país. Os dados a respeito do tempo de doença, contudo, de acordo com outros autores, são pouco confiáveis[11]. Eles dependem da lembrança do paciente e, muitas vezes, de sintomas prévios de otalgia, otorreia ou hipoacusia associados ao histórico de otite média recorrente ou otite secretora crônica, que podem ser facilmente confundidos com os sintomas do colesteatoma. Um estudo de Aberg e colaboradores[12], que comparou as queixas clínicas de pacientes com OMC colesteatomatosa e não colesteatomatosa, por meio de questionário entre os dois grupos, não encontrou diferença nos sintomas. Isso pode explicar a grande diferença na média do tempo desde o início dos sintomas entre crianças e adultos, já que muitos adultos apontam o início das suas queixas na infância.

As malformações de palato são um fator de risco conhecido para o desenvolvimento do colesteatoma. Dominguez e colaboradores[6] estimaram que o risco de colesteatoma em uma criança com fenda palatina é de 2,6% a 9,2%. Spilsbrury e colaboradores[13], estudando crianças que foram submetidas à colocação de tubo de ventilação pelo menos uma vez, observaram que 6,9% das

com fenda palatina desenvolveram colesteatoma em comparação com 1,5% das sem fenda. Harris e colaboradores[14] observaram uma incidência de colesteatoma entre os 5 e os 18 anos de idade em 2,2 % dos pacientes submetidos à palatoplastia, sendo essa taxa 200 vezes maior do que a observada na população em geral. Um estudo prévio do nosso grupo demonstrou uma prevalência de colesteatoma de 6,4% em pacientes com fissura labiopalatina ou palatina isolada[15]. Já no presente estudo, observamos uma frequência de 4,3% de pacientes com malformações de palato, não havendo diferenças entre crianças e adultos, enquanto Kemppainen e colaboradores[5], estudando 500 pacientes com colesteatoma, encontraram uma prevalência de 8%.

Na nossa casuística, 54,9% dos pacientes foram submetidos à cirurgia no período de realização do estudo. Como o nosso serviço é referência estadual no tratamento da OMC, pela volumosa demanda de pacientes e poucos horários cirúrgicos, há uma grande demora desde a primeira avaliação até a cirurgia. O longo tempo de espera para a realização do procedimento e a maior progressão da doença decorrente dessa demora, associados à falta de adesão e à dificuldade de seguimento de alguns pacientes, faz com que a timpanomastoidectomia aberta seja a técnica cirúrgica de eleição. Na nossa rotina, indicamos a timpanomastoidectomia aberta nas seguintes situações: doença localmente avançada, comprometimento dos quadrantes póstero-superiores da orelha média que impeça a limpeza adequada do recesso do nervo facial e seio timpânico; mastoide esclerótica ou ebúrnea; orelha única; e/ou orelha contralateral com colesteatoma avançado ou com cavidade prévia.

Estudos epidemiológicos como este, realizado com uma série grande de pacientes, nos fornece dados a respeito da população do nosso país,

especialmente daquela que depende do sistema público de saúde e, com isso, permite a verificação da validade externa de estudos internacionais e de sua aplicabilidade e reprodutibilidade nos nossos pacientes.

Conclusão

Na nossa população, o colesteatoma foi mais frequente em adultos do que em crianças. Colesteatoma bilateral foi observado em 16.9%. Hipoacusia, associada ou não a otorreia, foi a queixa principal, e a grande maioria dos pacientes apresentava otorreia no momento da primeira avaliação. A prevalência de colesteatomas mesotimpânicos posteriores e epitimpânicos posteriores foi muito semelhante, e a frequência de malformações palatinas foi de 4,3% e similar entre crianças e adultos. Na maioria dos pacientes submetidos à cirurgia, a timpanomastoidectomia aberta foi o procedimento de escolha.

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Cholesteatoma growth patterns: A critical review and a proposal of a new classification system

**Short running head: Cholesteatoma growth patterns

Letícia Schmidt Rosito, MD*; Luciana Netto, Sady Selaimen da Costa, PhD;

Department of Otolaryngology - Head and Neck Surgery, Hospital de Clinicas de Porto Alegre.
Department of Otolaryngology - Head and Neck Surgery , Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil.

*Correspondence and reprint requests author.: Letícia Schmidt Rosito, Department of Otolaryngology - Head and Neck Surgery. Hospital de Clinicas de Porto Alegre, Av. Ramiro Barcelos 2350, Porto Alegre, Rio Grande do Sul, CEP 90035-903, Brasil zipcode 90035903.

Phone: 55-51-96-69-8796;

E-mail: leticiarosito@gmail.com

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Abstract

Objective: Several classifications of cholesteatoma exist, but there are controversies about their clinical application. In this study, we aimed to review the existing classification systems and to propose a comprehensive new one.

Study Design: Cross-sectional comparative study.

Setting: A tertiary hospital.

Patients: We included 414 ears of 356 consecutive patients with middle ear cholesteatoma with no history of surgery.

Intervention: Otoendoscopy was conducted and findings for both ears were recorded.

Main Outcome Measure: Cholesteatoma growth patterns were classified into anterior epitympanic, posterior epitympanic, posterior mesotympanic, two routes, and undetermined.

Results: Posterior epitympanic (34.3%) and posterior mesotympanic (33.8%) were the most frequent types of cholesteatoma observed, followed by undetermined (16.2%) and two routes (13.8%). Anterior epitympanic type was the least frequent (2%). Posterior epitympanic cholesteatoma was more prevalent in adults (41.9%), whereas posterior mesotympanic cholesteatoma was more frequent in children (43.7%, $p < 0.0001$). Anterior epitympanic cholesteatoma was only observed in children.

Conclusion: Classifying cholesteatomas according to growth pattern into anterior epitympanic, posterior epitympanic, posterior mesotympanic, two routes, and undetermined includes all existing types of middle ear cholesteatoma. In general, the prevalence of posterior epitympanic and posterior mesotympanic cholesteatoma were similar. Whereas anterior epitympanic and the posterior

mesotympanic cholesteatomas were more prevalent in children, the posterior epitympanic was more frequent in adults.

Keywords: cholesteatoma;mastoid; middle ear; tympanic membrane retraction

Introduction

Cholesteatoma is characterized by the accumulation of exfoliated keratin debris in the middle ear or other pneumatized areas of the temporal bone [1]. Since cholesteatoma was first described, many classifications have being proposed. In principle, it is accepted that cholesteatomas can be classified into two categories: congenital and acquired [2]. As congenital cholesteatomas are very rare, the existent classifications are applied to the acquired type. The classifications are based on otomicroscopic appearance [3], typical growth patterns [4], disease extension [5], surgical findings [1], and otoscopic drum status [6]. However, there are still controversies about the clinical application of each of those classifications. In our view, the classification proposed by Jackler in 1989 [4] is the most embracing because it considers the different growth patterns, the diverse progression routes into middle ear and mastoid, and the typical ossicular erosion of each type of cholesteatoma. [4,9]. Although studies have systematically pointed the attic or posterior epitympanic cholesteatoma as the most frequent [4,7], a more recent study observed a greater prevalence of pars tensa cholesteatoma [6].

Regarding the age group, several studies have pointed significant differences between cholesteatomas in children and in adults [8-13]. Some authors have hypothesized that cholesteatomas in children may be more aggressive [8,9] and can present a higher tax of recurrence after surgery [10-13]. There has been, however, no report if cholesteatomas in children and adults are different according to prevalence of the typical growth patterns

In this study, we aimed to review the existing classification systems and to propose a comprehensive new one based on videotoscopic appearance and

pathogenesis; to describe the prevalence of the cholesteatoma subtypes; and to verify if there are differences between children and adults.

Methods

We included 414 ears of 356 consecutive patients that met the inclusion criterion in the monitoring period from August 2000 to March 2013. The patients selected for this study were outpatients treated at a tertiary hospital. Detailed clinical history was obtained and otologic examination was performed. Careful and detailed cleaning of the ear canal was performed prior to the examination. Fiberoptic otoendoscopy (0° and 4 mm; Karl Storz Endoskope) in both ears was recorded sequentially with CyberLink PowerDirector software (version 7; CyberLink).

The inclusion criteria were the presence of cholesteatoma in at least one middle ear.

The exclusion criteria were as follows: refusal to participate in the study; a previous history of any ear surgery except tympanostomy for ventilation tube placement; and impossibility of cleaning and performing videotoscopy for appropriate documentation.

The recorded images were independently reviewed by the same researcher. Cholesteatoma growth pattern was classified following a modified version of Jackler classification, with the addition of two-route and undetermined subtypes [4]:

1. Attic or posterior epitympanic (when the cholesteatoma is confined to the pars flaccida, figure 1);

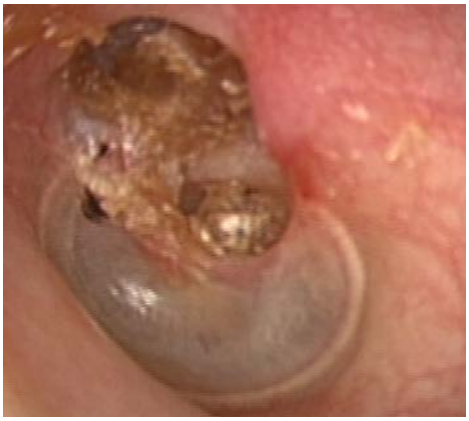

Figure 1: *Posterior epitympanic cholesteatoma*

2. Tensa or posterior mesotympanic (when the cholesteatoma arises in the posterosuperior quadrant of the pars tensa, figure 2);

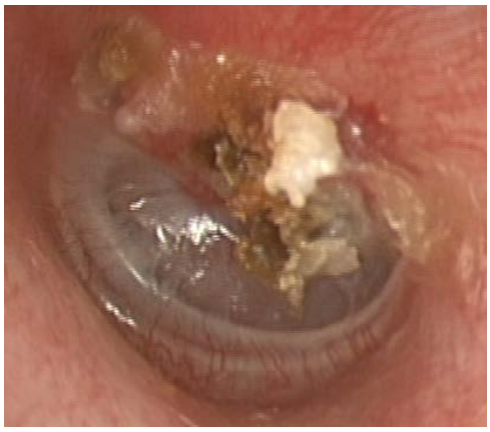

Figure 2: *Posterior mesotympanic cholesteatoma*

3. Anterior epitympanic (when the cholesteatoma originates cranially and anteriorly to the malleus head, figure 3);

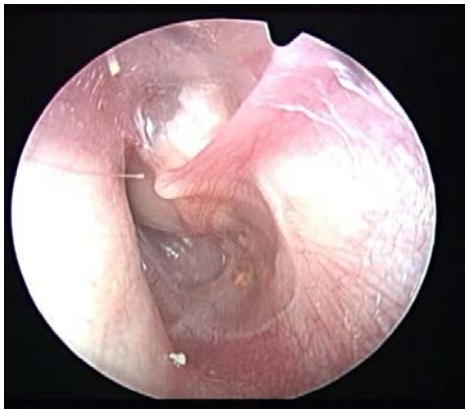

Figure 3: *Anterior epitympanic cholesteatoma*

4. Two-route or posterior epitympanic and mesotympanic (when both the pars flaccida and the pars tensa are involved, figure 4);

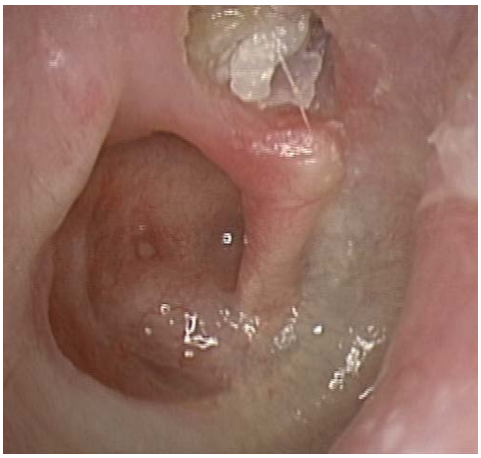

Figure 4: *Two-routes cholesteatoma*

5. Undetermined (when the precise growth pattern could not be identified by videotoscopy, figure 5).

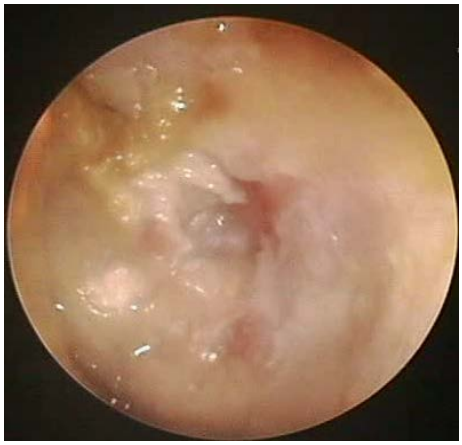

Figure 5: *Undetermined cholesteatoma*

The procedures followed were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration. The hospital's Research Ethics Committee approved this study (protocol number 14918). All participating patients, or their parents or guardians where the participant was a child, provided written informed consent prior to their inclusion in the study.

Statistical analysis using chi-square test and Fisher's exact test was performed using SPSS Statistics software (version 20). Statistical significance was set at $p < 0.05$.

Results

The mean patient age was 33.23 years (standard deviation [SD], 19.81; range, 4–82 years) and 125 (51.7%) patients were female. The right ear was identified as the affected ear in 220 (53.1%) patients. A total of 272 (65.7%) ears were from adults.

The prevalence of cholesteatoma growth patterns in the study population is shown in Figure 6.

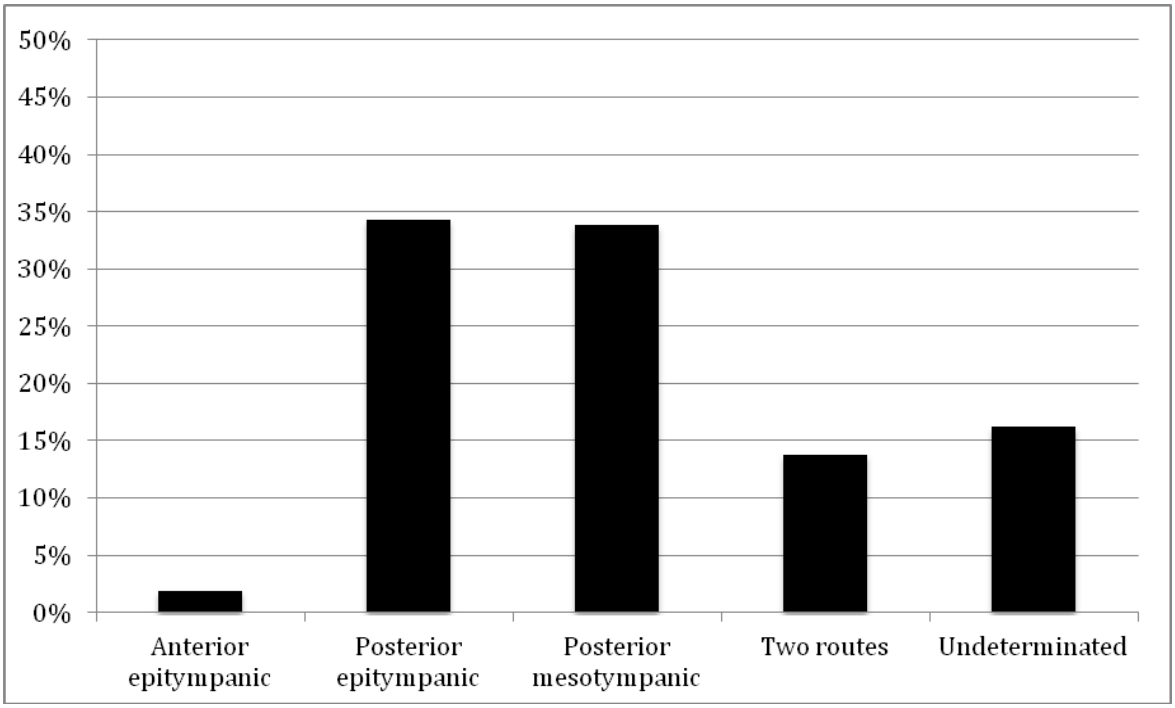

Figure 6: *Prevalence of cholesteatoma growth patterns among the study population.*

Posterior epitympanic (34.3%) and posterior mesotympanic (33.8%) were the most frequent cholesteatomas observed, followed by undetermined (16.2%) and two routes (13.8%). Anterior epitympanic type was the least frequent (2%).

When we compared children with adults, they were similar in gender frequency (percentage of males, 40.8% vs. 49.6%, respectively; $p = 0.097$) and affected ear (percentage of right-side affected ear, 47.1% vs. 52.9%, respectively; $p = 0.918$).

However, in terms of cholesteatoma growth patterns, posterior epitympanic was more prevalent in adults (41.9%), whereas anterior epitympanic (4.9%) and posterior mesotympanic (43.7%) were more prevalent in children ($p < 0.0001$). In fact, anterior epitympanic cholesteatoma only occurred in children. The prevalence

of two routes and the undetermined cholesteatoma was similar between the two groups (Figure 7).

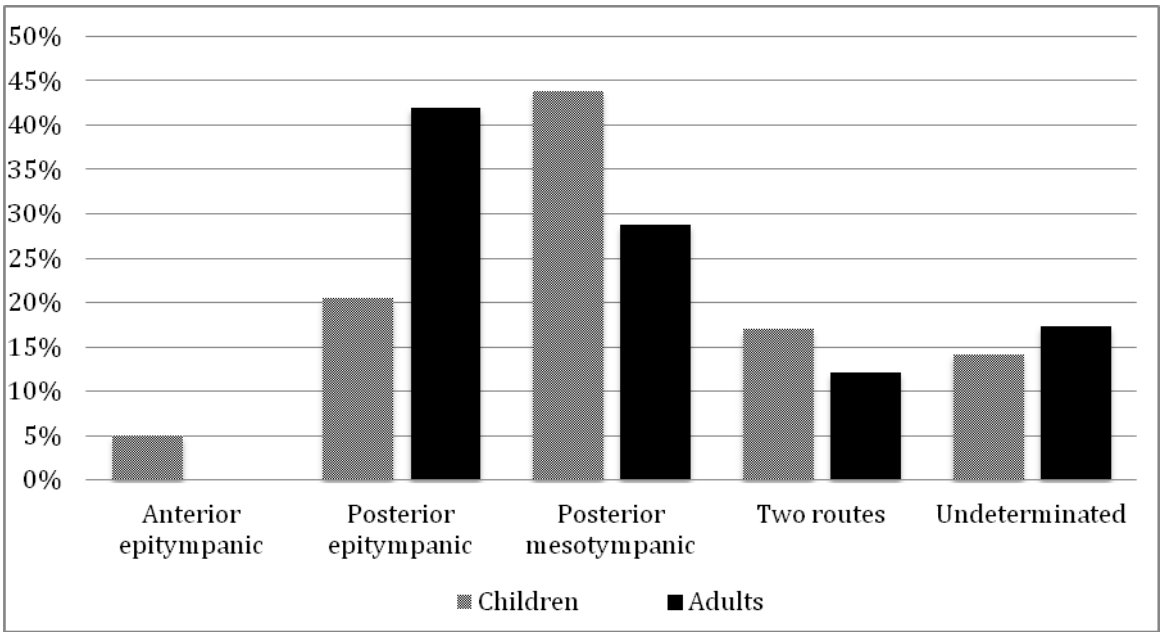

Figure 7: *Prevalence of cholesteatoma growth patterns in children and adults.*

Discussion

Acquired cholesteatomas are classically divided into attic, originating from Shrapnell's membrane, and sinus, originating from the posterosuperior retraction of the pars tensa [14]. Later, Tos [15] proposed a widely accepted classification that further subdivided the pars tensa cholesteatoma into sinus cholesteatoma, with primarily posterior retraction and posterior pathology, and into tensa retraction cholesteatoma, with primary retraction of the entire pars tensa and primary pathology both in anterior, inferior, and posterior parts of the tympanic cavity.

Comparing Tos [15] and Jackler [4] classifications, posterior epitympanic cholesteatoma is the equivalent to attic cholesteatoma. According to Jackler, this route is the most common and passes through the superior incudal space, which lies lateral to the incus body, and then traverses the aditus ad antrum to enter the

mastoid. It usually reaches the middle ear by descending through the floor of Prussak's space into the posterior pouch of von Troeltsch. In our study, we observed similar prevalence of posterior epitympanic and posterior mesotympanic cholesteatomas (34.3% vs. 33.8%, respectively). These findings are in agreement with a previous study that found a prevalence of 45% for pars tensa and 41% for attic cholesteatoma [6].

When we analyze the pars tensa cholesteatoma, however, the classifications diverge. While Jackler [4] considered only posterior mesotympanic cholesteatoma, originating from the posterior portion of the pars tensa retraction, Tos [9] subdivided it into sinus, which is the equivalent to posterior mesotympanic, and tensa. We agree with the posterior mesotympanic concept as it refers to a typical route of extension in which, in contrast to posterior epitympanic, the mastoid progression of cholesteatoma typically passes medial to the malleus and incus, and the sinus tympani and facial recess are commonly involved. When the entire area of the middle ear is affected by the cholesteatoma, however, it is difficult to determine precisely if the disease is the result of a complete pars tensa atelectasis (tensa cholesteatoma) or if it was a posterior mesotympanic or even a posterior epitympanic that had advanced to others compartments. For such reason, we preferred to classify unknown cases as undetermined.

It is not unusual for multiple cholesteatoma sacs to occur in the same ear involving two or even all the typical routes [4]. Passing through the anterior tympanic isthmus is the main route of drainage and aeration of the attic rooms and can be occluded by mucosal edema, thick mucus plugs, or even retraction of the posterior portion of the pars tensa, ultimately resulting in ventilation problems also in the epitympanum [16–18]. Black [6] reported a prevalence of 14% of combined

attic–pars tensa cholesteatoma, which we named two routes. In our study, the prevalence of two routes types was 13.8%.

The classification of cholesteatomas into congenital and acquired is very useful, since it separates two types of cholesteatoma with distinct pathogenesis and biological behavior. However, sometimes it is difficult to determine clinically if the it is congenital or acquired. First, congenital cholesteatoma is rare, accounting for approximately 4% of childhood and 2–5% of all cholesteatomas [19,20]. Secondly, the classic definition of Derlacki and Clemis [21] of congenital cholesteatoma as a pearly mass medial to an intact tympanic membrane, a normal pars tensa and pars flaccida and no history of otorrhea, tympanic membrane perforation or previous otologic procedures have been questioned mainly because children with congenital cholesteatoma can have middle ear infections and associated complications [22]. In our study, we found a prevalence of 4.9% of anterior epitympanic cholesteatoma. This cholesteatoma growth pattern was only described by Jackler [4], as a epitympanic retraction that forms anterior to the malleus head following the embryologic course of either the saccus anticus or the anterior saccule of saccus medius. In our study, all the cases were observed in children. Moreover, in a previous analysis, we observed that all the contralateral ears of these patients were normal (unpublished dada). For that reasons, we hypothesize that this cholesteatoma growth pattern is congenital, even with pars flaccida retraction and history of otorrhea. The most prevalent location of congenital cholesteatomas has been reported as lying within the anterosuperior quadrant [23], and the most accepted theory about its formation, the epithelial rest theory, is based in the presence of epidermoid residues in the anterosuperior quadrant of the fetal middle ear [24]. The development of cholesteatoma in this

specific position can lead to obliteration of the anterior portion of the tympanic isthmus, which in healthy ears is an open structure with no fold [25]. This obliteration can cause pars flaccida retraction or the cholesteatoma can simply expand superiorly and erode the attic.

Besides the finding that anterior epitympanic cholesteatoma only occurred in children, we also observed that pediatric patients had a higher prevalence of posterior mesotympanic while adults had a greater prevalence of posterior epitympanic cholesteatoma. Chronic otitis media with effusion is very frequent in children, mainly caused by Eustachian tube dysfunction. If poor middle ear ventilation persists, it is possible that some cases progress over the time to moderate and severe posterior pars tensa retraction and then, in the absence of mechanisms to stop the process, to bone erosion and keratin accumulation. Although the pars flaccida is more fragile and thus more susceptible to retraction, the progression of the disease seems to depend on 1) a preexistent, maybe congenital, alteration of the attic ventilation routes and 2) a longer time for disease development, when compared with posterior mesotympanic cholesteatoma. These can be the reasons why, even if both pathological processes can been initiated in the childhood, pars tensa tympanic membrane retractions can progress more easily to cholesteatoma formation, occurring earlier in the patient's life, than attic retractions.

After the critical review of cholesteatoma classifications, it seems to us that the classification proposed by Jackler is the most encompassing. The cholesteatoma classification, based in both videotoscopy and disease pathogenesis, into anterior epitympanic, posterior mesotympanic, two routes, and undetermined, however, includes all the existing types of middle ear

cholesteatoma. In our study population, the prevalence of posterior epitympanic and posterior cholesteatoma were similar. Anterior epitympanic and posterior mesotympanic cholesteatomas were more prevalent in children, whereas posterior epitympanic cholesteatoma was more frequent in adults.

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Conflict of interest

The authors disclose no conflicts of interest**.**

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Hearing impairment in children and adults with acquired middle ear cholesteatoma: Audiometric comparison of 385 ears

**Short running head: Hearing loss in cholesteatoma

Letícia Schmidt Rosito, MD*; Luciana Netto, Sady Selaimen da Costa, PhD;

Department of Otolaryngology - Head and Neck Surgery, Hospital de Clinicas de Porto Alegre,

Department of Otolaryngology - Head and Neck Surgery , Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil.

*Correspondence and reprint requests author.: Letícia Schmidt Rosito, Department of Otolaryngology - Head and Neck Surgery. Hospital de Clinicas de Porto Alegre,

Av. Ramiro Barcelos 2350, Porto Alegre, Rio Grande do Sul, CEP 90035-903,

Brasil zipcode 90035903.

Phone: 55-51-96-69-8796;

E-mail: leticiarosito@gmail.com

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Abstract

Objective: Evaluate hearing impairment in acquired middle ear cholesteatoma and investigate audiometric differences between children and adults.

Study design: Cross-sectional comparative study.

Setting: Tertiary hospital.

PatientsMethods: 323 Consecutive patients diagnosed with acquired middle ear cholesteatoma in at least one ear (385 ears) between August 2000 and March 2013 and no surgical history (mean [SD] age, 32.8 [19.4] years; 54.3% men and 34.8% children).

Intervention: Pure tone audiometry.

Main outcome measures: Air-conduction (AC) and bone-conduction (BC) thresholds and air–bone gaps (ABGs) measured at the pure tone average (PTA) and individual frequencies.

Results: The mean AC and BC thresholds at the PTA were 46.8 (22.7) and 17.7 (17.5) dB, respectively. The mean ABG at the PTA was 29.6 (13.4) dB, and that at 500 Hz was significantly greater than the ABGs at the other frequencies. Only 3.6% of the ears had profound hearing loss, without a significant difference between children and adults. The AC and BC thresholds were significantly greater in adults at all the frequencies ($p \leq 0.05$), but the ABGs were not significantly different between the age groups.

Conclusion: Acquired middle ear cholesteatoma is associated with significant hearing impairment, although profound hearing loss is rare. Adults have greater AC and BC thresholds than children but similar ABGs to children.

Keywords: audiometry, pure-tone; hearing loss; cholesteatoma, middle ear; age distribution.

INTRODUCTION

Acquired middle ear cholesteatoma is a gradually expanding destructive epithelial lesion of the temporal bone, resulting in progressive erosion of adjacent bony structures (1). Its most common origins, based on otomicroscopic or videotoscopic findings, are the pars flaccida (attic cholesteatoma) and posterosuperior quadrant of the pars tensa (posterior mesotympanic cholesteatoma) (2,3). In both cases, the lesion overgrows and erodes the fragile ossicular chain, contributing to the conductive hearing loss perceived by most patients. Although auditory function is a concern for both patients and surgeons, the mechanism of hearing loss in cholesteatoma and its consequences are still poorly understood.

Recent studies of hearing loss associated with cholesteatoma were more focused on comparing surgical outcomes between children and adults (4) than on the distinct pathogenesis and clinical and audiological differences of cholesteatoma according to age. In particular, knowledge of the magnitude of hearing impairment, mostly affecting audiometric frequencies and repercussion at the pure tone average (PTA), could help us to understand the pathogenesis of this disease better. The objectives of this cross-sectional study were to evaluate hearing impairment in acquired middle ear cholesteatoma and investigate audiometric differences between children and adults.

MATERIALS AND METHODS

The subjects were patients diagnosed with acquired middle ear cholesteatoma at a tertiary hospital between August 2000 and March 2013. The

study protocol was approved by the hospital's Research Ethics Committee under number 14918 and conformed to the tenets of the Helsinki Declaration. Adult patients and parents or guardians of children signed informed consent forms before the study.

For every patient, a detailed clinical history was recorded and otological examinations were performed after carefully cleaning the ear canals. Fiber-optic otoendoscopy (0° and 4 mm otoendoscope, Karl *Storz GmbH,* Tuttlingen, Germany) was performed in both the ears and images were recorded sequentially with PowerDirector version 7 (CyberLink Corporation, Taipei, Taiwan).

The inclusion criterion was presence of acquired cholesteatoma in at least one middle ear. Exclusion criteria were history of any ear surgery except tympanostomy for ventilation tube placement, and impossibility of cleaning and videotoscopy for appropriate imaging.

All the patients underwent pure tone audiometry (AD 27 audiometer, Interacoustics AS, Assens, Denmark; TDH-39 supraural earphones, Telephonics *Corporation, Farmingdale, NY*). For measuring bone-conduction (BC) thresholds, a BC transmitter was placed on the mastoid bone. Narrow-band masking noise was applied when needed. In young children, in whom reliable measurements can be problematic, play-conditioned audiometry with supraural earphones was performed. When necessary, pure tone audiometry was concluded after two sessions to confirm the results.

Air-conduction (AC) thresholds were measured at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz. BC thresholds were measured at 500, 1000, 2000, 3000, and 4000 Hz. Air–bone gaps (ABGs) were calculated from the

differences between the AC and the BC thresholds. The PTAs of the AC and BC thresholds and ABGs were calculated as the mean of 500, 1000, and 2000 Hz.

For audiometric comparisons, the study population was divided into the pediatric group, comprising patients aged 0 to 18 years, 11 months, and 30 days (United Nations Convention on the Rights of Children, 1989), and the adult group, with patients aged 19 years and older. Statistical analysis was performed by using SPSS software (SPSS, Chicago, IL). Qualitative variables were analyzed by chi-square or Fisher's exact test. Quantitative variables were compared with the Mann–Whitney *U*-test or Wilcoxon test, when indicated. All tests were two-tailed, and the level of significance was set at $p \leq 0.05$.

RESULTS

Three hundred eighty-five ears of 323 patients were tested (Table 1).

Characteristic	Value
Age (years), mean (standard deviation; range)	32.81 (19.41; 3–82)
Men	209 (54.3)
Children	134 (34.8)
Right ear	204 (53.0)
Cholesteatoma growth pattern	
Anterior epitympanic	7 (1.8)
Posterior epitympanic	130 (33.8)
Posterior mesotympanic	134 (34.8)
Two routes	54 (14)
Undetermined	60 (15.6)

Data represent number (%) unless otherwise indicated.

TABLE 1. *Clinicodemographic characteristics of the patients*

Posterior mesotympanic cholesteatoma was more prevalent in the pediatric group (41.6% vs. 28.3%), whereas posterior epitympanic cholesteatoma was more prevalent in the adult group (42.3% vs. 21.2%; $p < 0.0001$).

The mean ABGs ranged between 21.93 dB at 3000 Hz and 33.93 dB at 500 Hz. The mean ABG at the PTA was 29.58 dB (Table 2).

Frequency (Hz)	Bone-conduction threshold	Air-conduction threshold	Air–bone gap
250		50.22 (22.02)	
500	15.69 (16.89)	49.82 (22.43)	33.93 (15.60)
1000	16.00 (17.99)	48.84 (23.34)	32.66 (15.58
2000	20.38 (19.23)	43.03 (24.49)	22.18 (13.54)
3000	24.45 (19.89)	47.23 (26.13)	21.93 (13.61)
4000	24.75 (20.69)	49.73 (25.90)	24.50 (14.39)
6000		55.58 (26.64)	
8000		53.78 (28.60)	
Pure tone average	17.71 (17.50)	46.88 (22.75)	29.58 (13.46)

Data represent mean (standard deviation) values (dB).

TABLE 2. *Pure tone audiometric data of the study population*

Further, 29.2%, 42.2%, and 23.6% of the study population had ABGs at the PTA under or equal to 20 dB, between 20 and 40 dB, and over 40 dB, respectively. The ABGs at 500 Hz were significantly greater than those at 1000, 2000, 3000, and 4000 Hz (Wilcoxon test; $p = 0.02$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). The ABGs at 1000 Hz were also significantly greater than

those at 2000, 3000, and 4000 Hz (Wilcoxon test; $p < 0.001$ in all cases). The ABGs at 2000 and 3000 Hz were significantly smaller than those at 4000 Hz (Wilcoxon test; $p < 0.001$ and $p < 0.001$, respectively) but were not significantly different from each other (Wilcoxon test; $p = 0.74$).

The mean AC thresholds varied between 43.03 dB at 2000 Hz and 55.58 dB at 6000 Hz. The mean BC thresholds varied from 15.69 dB at 500 Hz to 24.75 dB at 4000 Hz. The mean AC and BC thresholds at the PTA were 46.88 and 17.71 dB, respectively (Table 2). The prevalence of severe or profound hearing loss was 3.6% of all the cholesteatoma-affected ears.

The AC and BC thresholds were greater in the adult group at all the frequencies ($p < 0.0001$ in all cases). The ABGs, however, were similar between the groups, as demonstrated in Figure 1 ($p = 0.138$ at 500 Hz; $p = 0.634$ at 1000 Hz; $p = 0.477$ at 2000 Hz; $p = 0.498$ at 3000 Hz; and $p = 0.748$ at 4000 Hz).

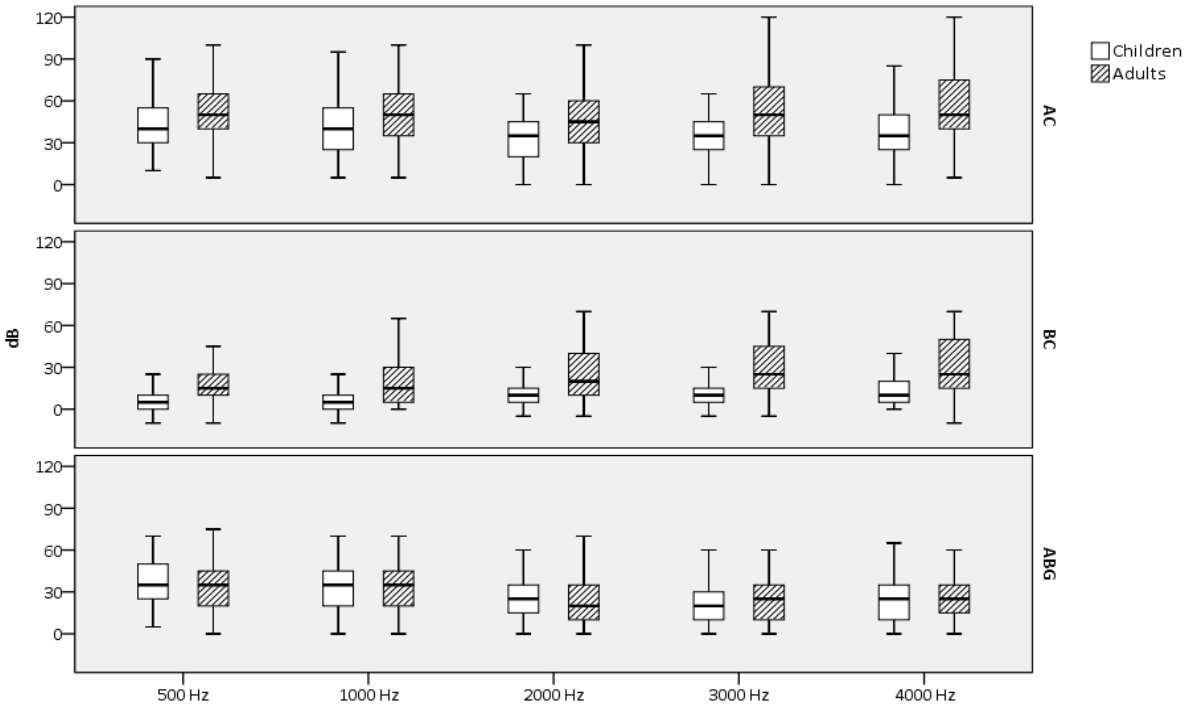

FIG. 1. *Bone-conduction (BC) and air-conduction (AC) thresholds and air–bone gaps (ABGs) in the pediatric and adult groups. The central horizontal lines and superior and*

inferior limits of the boxes indicate median values and interquartile ranges (75th and 25th percentiles), respectively.

A significant age-related difference in the ABGs at the PTA was not observed (p = 0.25; Fig. 2). The prevalences of profound hearing loss were almost the same in children and adults (3.7% vs. 3.6%; p = 1 by Fisher's exact test).

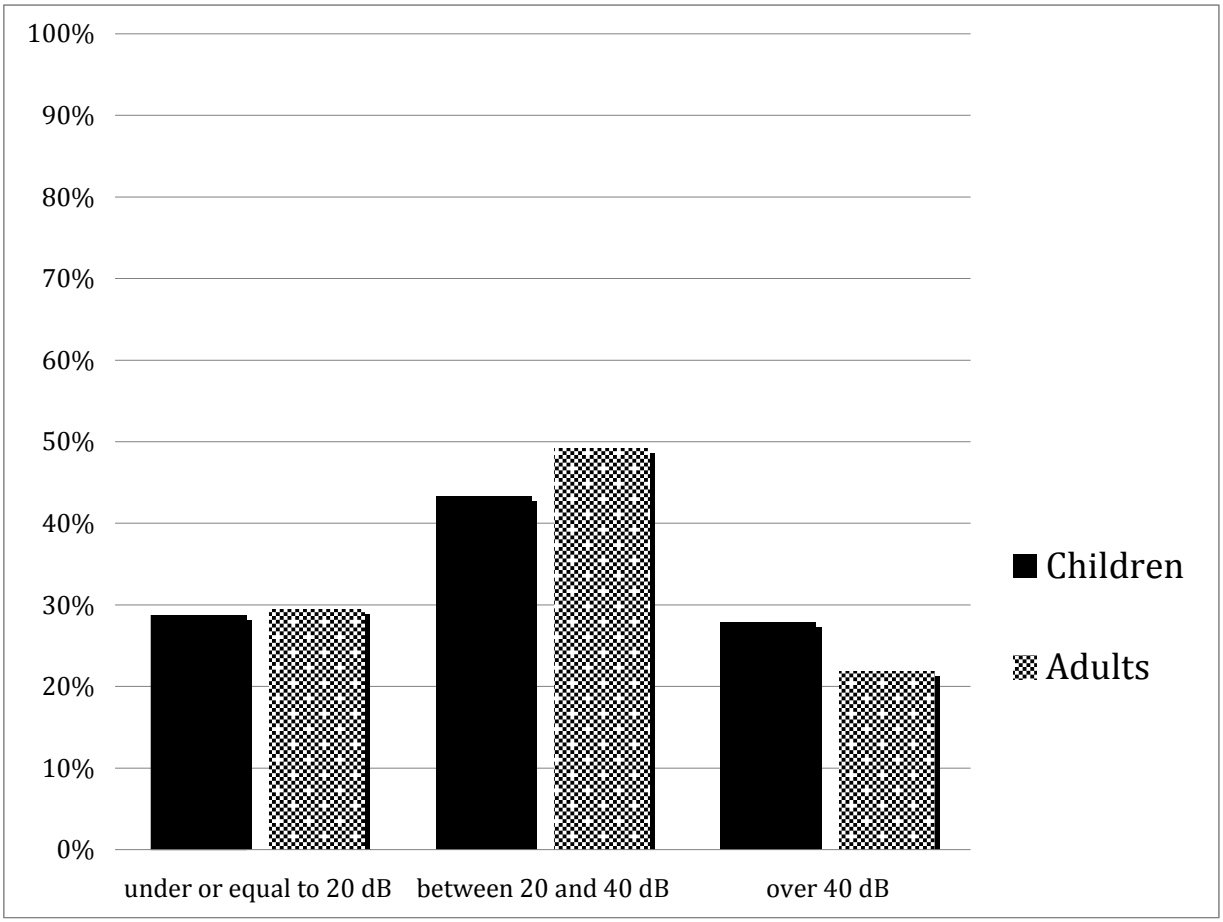

FIG. 2. *Prevalence of air–bone gaps at the pure tone average under or equal to 20 dB, between 20 and 40 dB, and over 40 dB in the pediatric and adult groups.*

DISCUSSION

This study demonstrated significant hearing impairment due to middle ear cholesteatoma. About 70% of the patients had ABGs at the PTA higher than 20 dB. In normal ears, gain in hearing due to ossicular coupling is frequency dependent, with the maximal gain occurring at 1 KHz (5), which can explain the finding of greater ABGs at lower frequencies. In general, an ABG is attributable to ossicular erosion. Martins et al. (6) noticed that erosion of each ossicle contributes, in a graded and independent manner, to increased ABGs in patients with acquired middle ear cholesteatoma, with the status of the incus having the most significant association with ABGs. They discussed that an ABG can often be measured in patients with cholesteatoma but without ossicular erosion by limiting the vibratory capacity of an intact ossicle or decreasing aeration of the middle ear and vibratory capacity of the tympanic membrane. The opposite is also true: patients with cholesteatoma and ossicular erosion can have minimal ABGs because the cholesteatoma can transmit the sound wave directly to the oval window.

BC and AC thresholds were different at all the tested frequencies between children and adults. These results can be explained, although not exclusively, by the natural aging process. The similar ABGs between the groups demonstrate that conductive hearing loss occurs equally in adults and children. In a study of only children and teenagers with chronic otitis media, Netto et al. (7) demonstrated that cholesteatoma significantly increases AC and BC thresholds as well as ABGs and lower frequencies are more compromised than higher ones. Although adults may have longer disease duration, with greater progression and ossicular erosion, cholesteatoma in children can be more aggressive. For example, Dornelles et al. (8) demonstrated that cholesteatoma in children presents a more exacerbated

inflammatory degree and produces more metalloproteinases. Further, the prevalence of complications (9) increases because the frequency of cholesteatoma recidivism (10,11) can rise in children. The aggressiveness and exacerbated inflammatory reaction could cause greater ossicular erosion and, consequently, earlier significant hearing loss in children.

Given the severity of hearing loss due to cholesteatoma, treatment should include not only techniques to eradicate the disease but also mechanisms to restore auditory function. Prostheses for ossicular chain reconstruction or bone-anchored hearing aids should be considered after cholesteatoma surgery. Moreover, management of sensorineural impairment, occurring mainly in adults, should also be considered, for which other options with greater BC gain must be developed.

In conclusion, acquired middle ear cholesteatoma is associated with significant hearing impairment, although profound hearing loss is rare. Adults have greater AC and BC thresholds than children, but ABGs are similar between the age groups.

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Sensorineural hearing loss in cholesteatoma

Short running head: Sensorineural hearing loss in cholesteatoma

Letícia Schmidt Rosito, MD*; Luciana Netto, Sady Selaimen da Costa, PhD;

Department of Otolaryngology - Head and Neck Surgery, Hospital de Clinicas de Porto Alegre,

Department of Otolaryngology - Head and Neck Surgery , Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil.

*Correspondence and reprint requests author: Letícia Schmidt Rosito, Department of Otolaryngology - Head and Neck Surgery. Hospital de Clinicas de Porto Alegre, Av. Ramiro Barcelos 2350, Porto Alegre, Rio Grande do Sul, CEP 90035-903, Brasil zipcode 90035903.

Phone: 55-51-96-69-8796;

E-mail: leticiarosito@gmail.com

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Abstract

Objective: To determine whether middle ear cholesteatoma is associated with sensorineural hearing loss, and whether patient age, cholesteatoma growth pattern, or air bone gap size contribute to inner ear impairment.

Study Design: Cross-sectional comparative.

Setting: A tertiary hospital.

Patients: The subjects were 115 patients with middle ear cholesteatoma in one ear, and normal video-otoscopy in the contralateral ear (CLE).

Interventions: Otoendoscopy, pure tone audiometry.

Main Outcome Measures: Bone conduction (BC) threshold differences between the normal CLE and the cholesteatoma ear. Comparisons of these differences between children and adults, and different cholesteatoma growth patterns. Correlation between the air bone gap size in the ear with cholesteatoma and the difference in bone conduction thresholds between both ears.

Results: The cholesteatoma ear was associated with greater BC thresholds than the CLE. Comparing children and adults, BC thresholds between the cholesteatoma ear and the CLE were different in both groups at all frequencies tested, except at 500 Hz in children. With regard to different cholesteatoma growth patterns, the differences between associated BC thresholds were also significant in all groups at all frequencies, with the exception of the two routes of cholesteatoma group at 500 Hz. Comparing BC threshold differences, they were greater in the adult group at 500 Hz. The correlation between the air bone gap

media in the ear with cholesteatoma and the difference in bone conduction thresholds between both ears was direct and moderate.

Conclusions: Cholesteatoma was associated with greater BC thresholds at all frequencies tested. The differences were observed in children and adults, and were independent of cholesteatoma growth patterns. As bigger the air bone gap in the ear with cholesteatoma, greater the inner ear damage.

Introduction

Middle ear cholesteatoma is a destructive disease that can aggressively spread and erode through the limits of the middle ear cleft and surrounding structures. Hearing loss of varying types can accompany cholesteatoma, but it is typically conductive in nature, secondary to ossicular erosion or impairment of normal ossicular mobility.[1]

The association between sensorioneural hearing loss (SNHL) and cholesteatoma is not well understood.[2] Although erosion of the capsula otic, most commonly involving the lateral semicircular canal, could be considered a clear mechanism of SNHL in cholesteatoma,[3] some authors have reported that labyrinthine fistula, a sporadic phenomenon, had no influence on functional cochlear lesions in chronic otitis media (COM) in their investigations.[2] However, when there is apparently no direct lesion into the inner ear produced by an existing cholesteatoma, the mechanisms responsible for sensorineural impairment and the magnitude of this damage are the source of even more debate.

The objectives of this study were to determine whether middle ear cholesteatoma is associated with SNHL, and to investigate whether patient age, cholesteatoma growth pattern, or air bone gap size contribute to inner ear impairment.

Materials and Methods

The current cross-sectional study included 115 consecutive patients diagnosed with COM with cholesteatoma, followed at the Chronic Otitis Media Center of the Hospital de Clinicas de Porto Alegre from August 2000 to March

2013. A detailed clinical history and otologic examination were completed for each patient. Careful and detailed cleaning of the ear canal was performed prior to the examination. Fiber-optic otoendoscopies of 0° and 4 mm (Karl Storz endoscope) were performed and recorded in both ears sequentially, with Cyberlink Powerdirector (version 7, 2008). The inclusion criterion was the presence of acquired cholesteatoma in one ear and normal video-otoscopy findings in the CLE. The exclusion criteria included refusal to participate in the study, history of any ear surgery other than tympanotomy for ventilation tube placement, and difficulty in cleaning or performing video-otoscopy for appropriate documentation.

All patients underwent pure tone audiometry and air conduction (AC) thresholds were determined at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz and BC thresholds and air bone gaps (ABG) at 500, 1000, 2000, 3000, and 4000 Hz. An Interacoustic AD 27 audiometer with supraural TDH-39 earphones was used. For BC thresholds, a BC transmitter placed on the mastoid bone was used. Even for AC and BC, narrow band masking noise was applied when needed. In young children, for whom problems in measuring reliable thresholds can arise, “playful conditioning” (play-conditioned audiomety with spraural earphone) was performed. When necessary, the pure tone audiometry could be concluded after two sessions in order to confirm its results. For comparisons, patients were divided into a pediatric group comprising patients aged ≤18 years 11 months 30 days (in accordance with the United Nations Convention on the Rights of Children, 1989) and an adult group of patients aged ≥19 years.

The findings of video-otoscopy were analyzed and the middle ear cholesteatomas were classified by the senior author by using a modified version of the method described by Jackler,[4] according to their growth pattern, into one of

the following: (a) posterior epitympanic (attical), (b) posterior mesotympanic (postero-superior quadrant of the pars tensa), (c) two routes (attical and mesotympanic), (d) indeterminate, and (e) anterior epitympanic.

The procedures followed were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration. The hospital's Research Ethics Committee approved this study (protocol number 14918). All participating patients, or their parents or guardians where the participant was a child, provided written informed consent prior to their inclusion in the study.

Statistical analysis was performed using SPSS (version 20) statistics software. To verify the SNHL associated with the disease by comparing BC thresholds between the cholesteatoma ear and the normal CLE, we used the nonparametric Wilcoxon test. To compare the sizes of the BC differences among the audiometric frequencies, we used the Friedman test and the multiple comparison by Student *t* distribution. To compare the sizes of the BC differences among the groups, we used the nonparametric Mann–Whitney test. To correlate air bone gap with the bonne conduction difference between the ear with cholesteatoma and the normal CLE, we used the 500 Hz, 1000 Hz , 2000Hz, 3000 Hz , and 4000 Hz threshold average and applied Person correlation test. All tests were two-tailed, and the level of significance was set at $p \leq 0.05$.

Results

One-hundred-and-fifteen patients met the inclusion criterion in the monitoring period. The characteristics of the total sample are shown in Table 1.

Age (years-old)	
Media, standard deviation (minimum and maximum)	32.40, 20.29 (3 -81)
Male sex n° (prevalence)	56 (48.7%)
Children n° (prevalence)	44 (38.3%)
Cholesteatoma growth pattern n° (prevalence)	
Anterior epitympanic	6 (5.2%)
Posterior epitympanic	37 (32.2%)
Posterior mesotympanic	40 (34.8%)
Two routes	11 (9.6%)
Undetermined	21 (18.3%)

Table 1: *Description of the patients included in the study*

Preoperative CT scan or surgical data were not available in 32 (27.8%) patients. In 70 (84.3%), the presence of labyrinthine fistula was analyzed via surgical data, and in 13 (15.7%), who had not been operated on yet, it was analyzed via CT scan. Fistula was found in 5 of these 83 patients (6%). In 4 of those 5 patients (80%) the fistula was localized on the lateral semicircular canal, and in 1 (20%) it was localized on the oval window. Labyrinthine fistula was observed in 1 (3.1%) child and 4 (9.1%) adults.

At all frequencies studied, the presence of cholesteatoma in the middle ear was associated with greater BC thresholds than in the CLE (Wilcoxon test, $p < 0.001$ at 500, 1000, 2000, 3000, and 4000 Hz) (Figure 1).

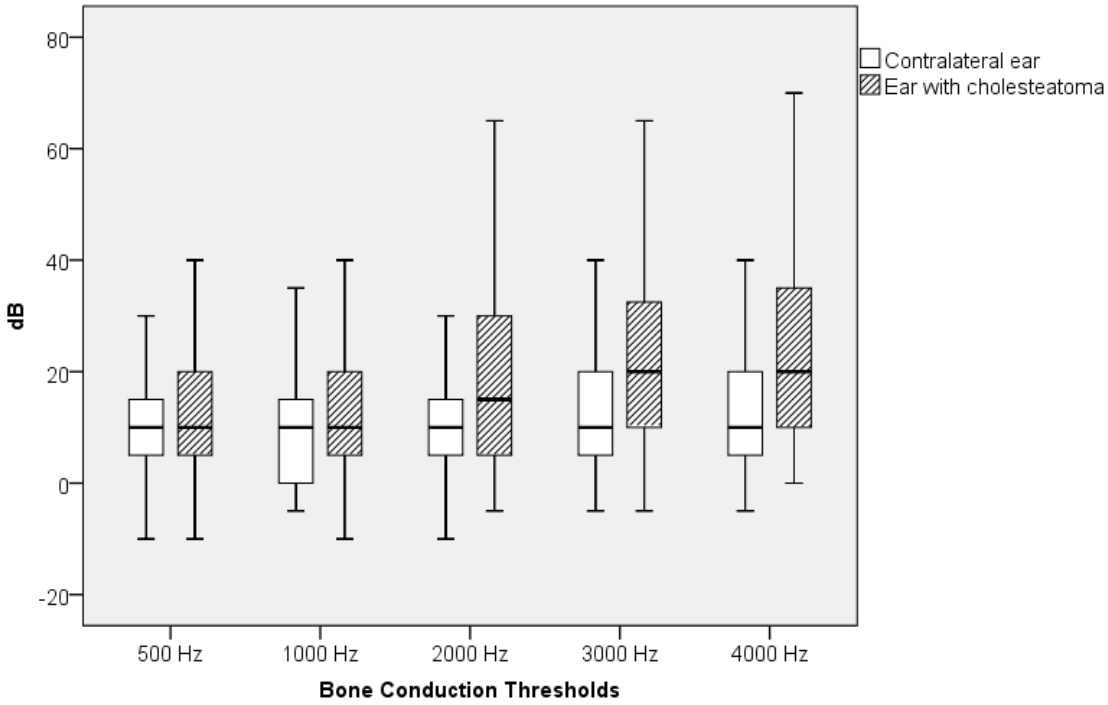

Figure 1: *Boxplot comparing the bone conduction thresholds between the ear with cholesteatoma and the normal contralateral. Median (black horizontal line inside the box), interquartile range (box superior limit (75th percentile)), and box inferior limit (25th percentile).*

Comparing the sizes of BC differences at the different audiometric frequencies, there were significant differences among them (p < 0.001). The median differences were 5 dB at 500 Hz, 1000 Hz, and 4000 Hz, and 10 dB at 2000 Hz and 3000 Hz. Multiple comparisons testing revealed that the BC differences between the cholesteatoma ear and the CLE were greater at 2000 Hz and 3000 Hz than at 500 Hz (p < 0.05). No significant differences were evident among the other frequencies.

Analyzing children and adults, the BC thresholds between the cholesteatoma ear and the CLE differed significantly in both groups at all frequencies, with the exception of 500 Hz in children (Table 2).

BC Fequency	Ear with cholesteatoma	Contralateral ear	P value
	Media (sd); median (ir)	Media (sd); median (ir)	
500 Hz			
Children (n=44)	5.58 (10.42); 5 (0-6,25)	3.08 (4,71); 5 (0-5)	0.098
Adults (n=73)	19.55 (14.93); 15 (10-25)	13.16(12.59); 10 (5-17.5)	**<0.001**
1000 HZ			
Children	7.12 (14.08); 5 (0-10)	2.50 (5.53); 0 (0-5)	**0.004**
Adults	20.80 (18.05); 15 (10-28.75)	12.98 (13.72) 10 (5-17.50)	**<0.001**
2000 Hz			
Children	9.42(13.75); 10 (0-10)	2.50 (5.70); 0 (0-6,25)	**<0.001**
Adults	24.91 (17.09); 20 (15-30)	15.88 (14.61); 10 (5-17.50)	**<0.001**
3000 Hz			
Children	13.80 (13.33); 10 (7.5-15)	6.00 (7.22); 5 (0-10)	**<0.001**
Adults	27.96(19.34); 22.5 (15-40)	21.16 (20.89); 15(10-25)	**<0.001**
4000 Hz			
Children	11.54 (13.77); 10 (5-15)	5.00 (6.33); 5 (0-10)	**0.002**
Adults	28.45 (20.23); 25 (10- 40)	22.02 (22.25); 15 (10-27.5)	**<0.001**

(sd) standard deviation; (ir) interquartile range

Table 2: *Comparison of bone conduction thresholds between the ear with cholesteatoma and the contralateral ear in children and adults.*

When we grouped the patients according to cholesteatoma growth pattern, the differences between the BC thresholds were also significant in all groups and frequencies, with the exception of the two routes cholesteatoma group at 500 Hz (Table 3).

BC Fequency	Ear with cholesteatoma Media (sd); median (ir)	Contralateral ear Media (sd); median (ir)	P value
500 Hz			
Posterior epitympanic (n=39)	17,31 (14,55); 15,00 (5-20)	11,18 (11,47); 10,00 (0-15)	**<0,001**
Posterior mesotympanic (n=39)	12,69 (15,34); 05,00 (0-20)	08,21 (10,67); 05,00 (0-10)	**0,008**
Two routes (n=11)	14,55 (21,15); 05,00 (0-25)	09,09 (8,31); 05,00 (5-15)	0,680
Indeterminated (n=22)	18,41 (15,84); 12,50 (8,75-31,25)	09,77 (8,50); 10,00 (3,75-15)	**0,003**
1000 HZ			
Posterior epitympanic (n=39)	16,67 (17,14); 10,00 (5-20)	09,61 (12,21); 07,50 (0-15)	**<0,001**
Posterior mesotympanic (n=39)	16,15 (18,93); 10,00 (5-20)	08,85 (11,95); 05,00 (0-10)	**<0,001**
Two routes (n=11)	19,09 (19,47); 15,00 (5-25)	09,09 (08,89); 10,00 (0-10)	**0,041**
Indeterminated (n=22)	19,09 (19,91); 10,00 (5-35)	10,23 (08,79); 10,00 (5-15)	**0,025**
2000 Hz			
Posterior epitympanic (n=39)	20,77 (17,11); 20,00 (10-25)	11,97 (12,81); 10,00 (3,75-15)	**<0,001**
Posterior mesotympanic (n=39)	19,10 (18,49); 15,00 (5-30)	11,28 (15,20); 05,00 (5-15)	**<0,001**
Two routes (n=11)	20,45 (19,80); 15,00 (5-30)	07,27 (06,84); 10,00 (0-10)	**0,011**
Indeterminated (n=22)	25,68 (21,89); 15,00 (10-46,25)	11,82 (12,96); 10,00 (5-16,25)	**0,001**
3000 HZ			
Posterior epitympanic (n=39)	24,05 (20,13); 20,00 (10-25)	15,81 (14,93); 10,00 (7,5-20)	**<0,001**
Posterior mesotympanic (n=39)	22,63 (17,92); 15,00 (10-30)	16,32 (22,62); 10,00 (5-21,25)	**<0,001**
Two routes (n=11)	26,50 (22,61); 20,00 (8,75-45)	10,00 (12,47); 05,00 (0-21,25)	**0,008**
Indeterminated (n=22)	28,64 (22,31); 20,00 (13,75-51,25)	14,09 (17,01); 12,50 (0-21,25)	**<0,001**
4000 Hz			
Posterior epitympanic (n=39)	23,59 (20,93); 20,00 (10-25)	18,16 (17,10); 15,00 (10-20)	**0,002**
Posterior mesotympanic (n=39)	21,84 (19,29); 17,50 (5-35)	14,74 (22,09); 10,00 (5-15)	**<0,001**
Two routes (n=11)	23,64 (23,56); 20,00 (5-40)	10,00 (16,88); 00,00 (0-20)	**0,025**
Indeterminated (n=22)	30,45 (24,29); 20,00 (15-60)	16,82 (18,22); 10,00 (5-30)	**0,022**

Table 3: *Comparison of bone conduction thresholds between the ear with cholesteatoma and the contralateral ear in the different cholesteatoma growth patterns.*

Comparing the BC threshold differences between the cholesteatoma ear and the CLE, the differences were greater in the adult group at 500 Hz (Mann–Whitney test, $p < 0.001$) and 2000 Hz (Mann–Whitney test, $p = 0.036$). At the other frequencies, they were similar (Mann–Whitney test, $p = 0.06$ at 1000 Hz, $p = 0.26$ at 3000 Hz, and $p = 0.11$) (Figure 2).

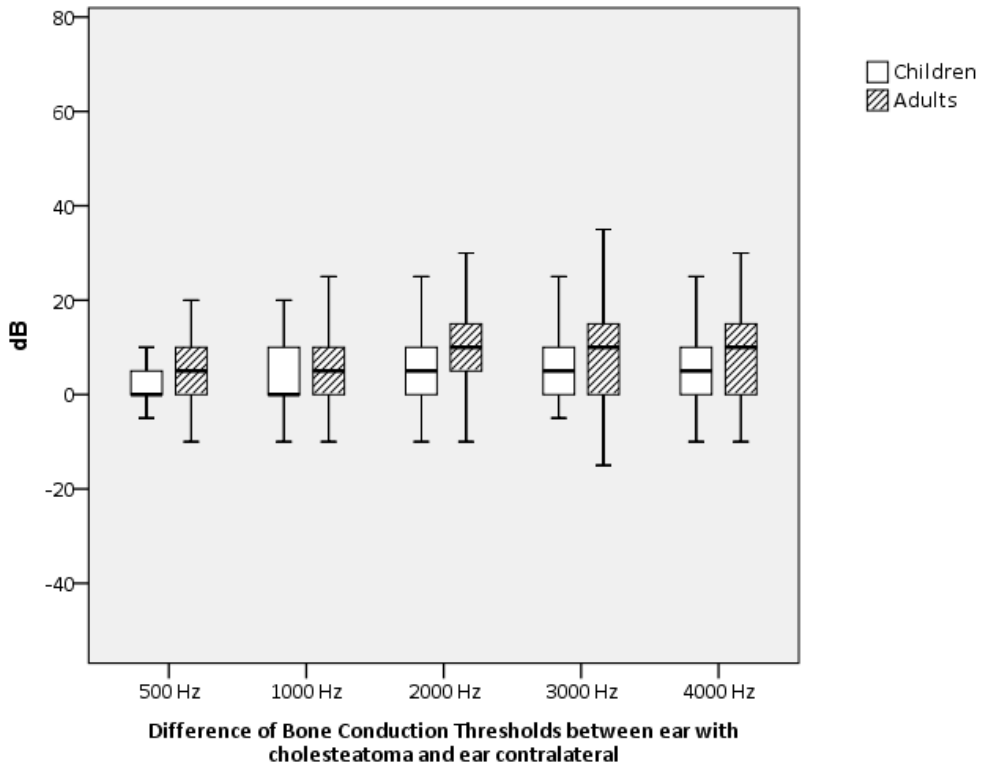

Figure 2: *Boxplot comparing the difference of bone conduction thresholds between the ear with cholesteatoma and the normal contralateral in children and adults. Median (black horizontal line inside the box), interquartile range (box superior limit (75th percentile), and box inferior limit (25th percentile).*

When we compared the BC differences between posterior epitympanic and posterior mesotympanic cholesteatomas, we did not find any significant differences at all between any of the frequencies (Mann–Whitney test, p = 0.64 at 500 Hz, p = 0.91 at 1000 Hz, p = 0.51 at 2000 Hz, p = 0.98 at 3000 Hz, and p = 0.34 at 4000 Hz) (Figure 3).

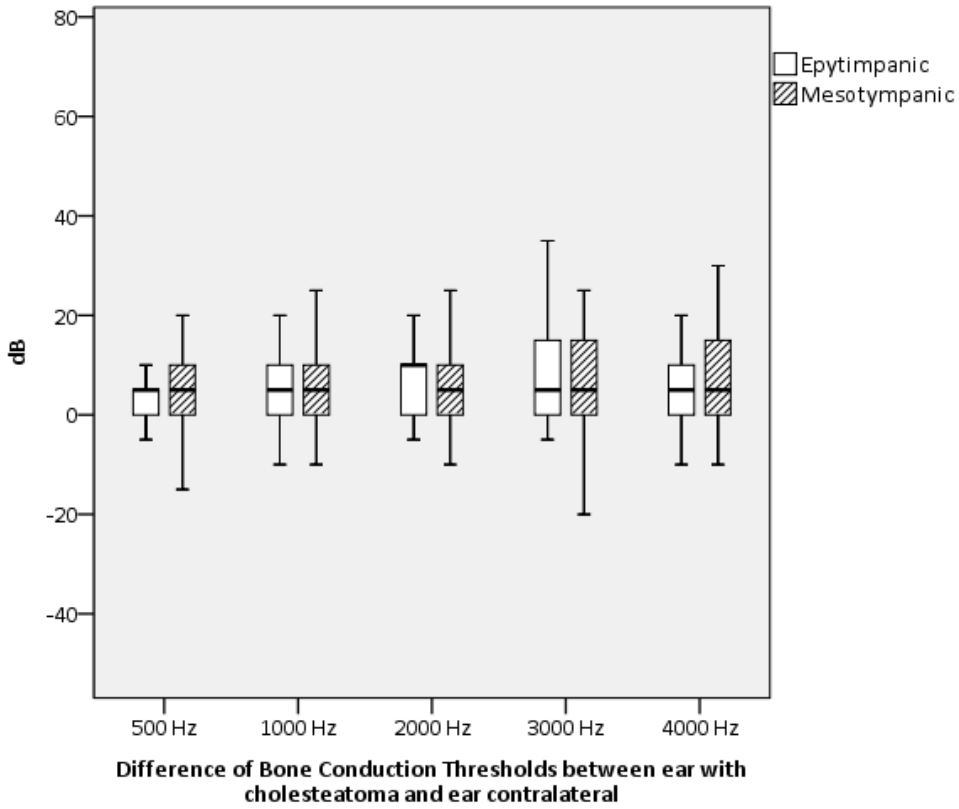

Figure 3: *Boxplot comparing the difference of bone conduction thresholds between the ear with cholesteatoma and the normal contralateral in posterior epitympanic and posterior mesotympanic cholesteatomas. Median (black horizontal line inside the box), interquartile range (box superior limit (75th percentile)), and box inferior limit (25th percentile).*

The Person correlation between the air bone gap average in the ear with cholesteatoma and difference of bone conduction thresholds average between the ear with cholesteatoma and the normal contralateral was R=0.64 (p=0.0001, figure 4).

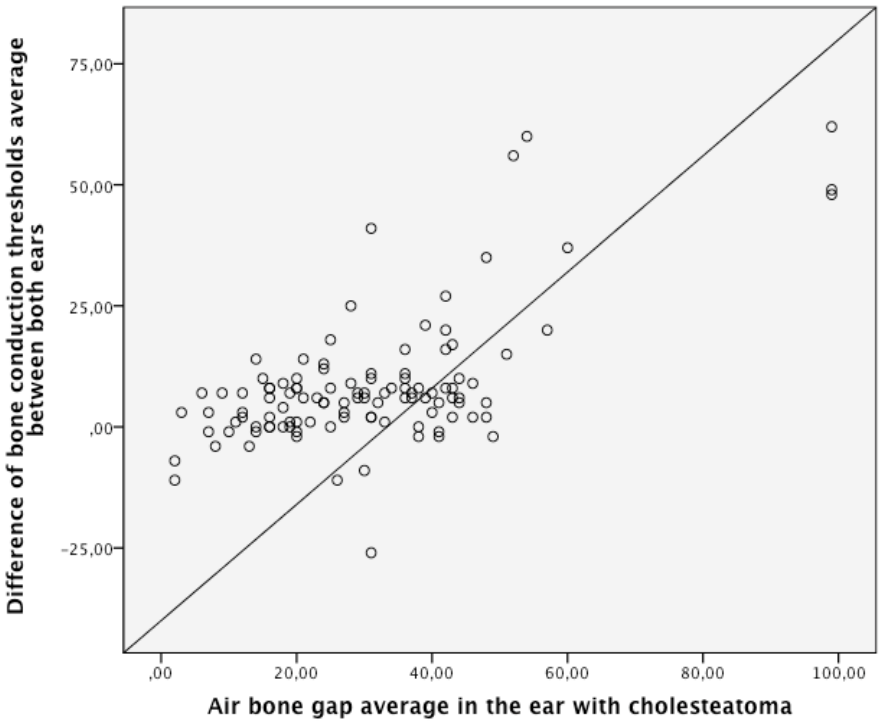

Figura 4: *Scatter of correlation between the air bone gap average in the ear with cholesteatoma and difference of bone conduction thresholds average between the ear with cholesteatoma and the normal contralateral.*

Discussion

We observed BC threshold differences between the cholesteatoma ear and the CLE at all frequencies tested, in both adults and children, except at 500 Hz in the latter group. This suggests that SNHL associated with cholesteatoma can occur in both age groups. Comparing adults and children, however, we observed greater BC differences in the adult group at 500 Hz and 2000 Hz. Redaelli de Zinis

et al.[2] observed, via a multivariate analysis in patients with COM, that the only factor associated with increasing BC thresholds at all frequencies analyzed was increasing age. In agreement with this finding, Eisenman and Parisier[1] found that with regard to BC pure tone average, there was significant difference in bone conduction thresolds between the ears (cholesteatoma vs. control) and age. The difference between the cholesteatoma and control ears, which varied across the age groups, appeared minimal in the youngest patients, largest in the middle-aged groups, and smaller in the older patients.

Cholesteatoma is well known to be the most aggressive type of COM, leading very often, [3] to labyrinthine bone destruction, fistula formation, and sensorineural hearing impairment. These authors reported a labyrinthine fistula frequency of 16.7%, mostly localized on the lateral semicircular canal, and mostly identified during surgery. We found a smaller frequency of fistula in our sample (6%), 80% on the semicircular canal, and 84.3% identified during the surgery, although approximately 27% of our sample had not been operated on at the time of data collection. Jesic et al.[3] did not find a correlation between the presence of labyrinthine fistulas and SNHL in patients with fistulas detected during surgery. However, in 2 patients with CT-visible labyrinthine destruction, whose audiograms showed moderate and severe SNHL, a significant influence of such labyrinthine fistulas on SNHL was found. These observations could mean that only large fistulas that can be easily identified on CT can lead to a greater sensorineural impairment. Thus, labyrinthine fistula is just one of several mechanisms by which cholesteatoma can cause damage to the inner ear.

The influence of inflammatory factors, mediators of inflammatory reactions, free radicals, and bacterial toxins on cochlear function have been well described.[5,6]

Paparella et al.[7] hypothesized that cochlear dysfunction associated with COM in the absence of direct invasion of the otic capsule was caused by penetration of inflammatory cells and mediators, via the round window membrane. Eisenman and Parisier[1] reported a significant interaural difference at 4000 Hz. They argued that if sensorineural dysfunction is a result of the passage of inflammatory mediators across the round window membrane, one might expect increased thresholds at higher frequencies such as 4000 Hz, tonotopically located at the basal turn of the cochlea, to appear before the lower more apically located frequencies are affected. Our results suggest that damage at 2000 Hz and 3000 Hz is greater than that at 500 Hz. However, the greatest effect was not observed at 4000 Hz in our study.

The presence of a cholesteatoma, frequently associated with longstanding middle ear inflammation and assumed to produce toxic and lytic enzymes from the active epithelium, has been suggested by some to pose a higher risk of the development of SNHL, independently of direct invasion of the inner ear.[1,8,9] In our previous study,[10] with only 47 patients with cholesteatoma, we demonstrated a significant difference in SNHL between patients with and without cholesteatoma, but only at 500 Hz. Jesic et al.[3] however, found that a predictive factor for SNHL appearance is COM itself, independent of pathology. After excluding patients with labyrinthine fistula, Redaelli de Zinis et al.,[2] also did not detect an association between cholesteatoma and increasing BC thresholds.

In our study, we observed significant differences between the cholesteatoma ear and the CLE for all cholesteatoma growth patterns. Thus, inner ear impairment can occur irrespective of the location or propagation route of the cholesteatoma. Another factor that can contribute to sensorineural damage is the duration of the disease.[2] Jesic et al.[3] did not detect a correlation between the

duration of cholesteatoma and SNHL. We agree with these authors, that the objectivity of the estimation of disease duration is questionable because it is mainly based on anamnestic data and subjective symptoms. Furthermore, patients can easily confuse a previous history of recurrent otitis media with the development of cholesteatoma. For that reason, we did not analyze this factor in our study.

The use of topical antibiotics may contribute to the development of SNHL in some cases, however there is little evidence to support it. While animal studies have demonstrated that compounds containing aminoglycosides can cause inner ear damage,[11,12] the few cases described in humans have associated the use of topical antibiotics only with COM without cholesteatoma, more specifically in dry tympanic membrane perforations.[13,14] In addition, the thickening of the mucous membrane in the middle ear due to chronic inflammation, as well the presence of cholesteatoma and secretion, may reduce the drug's absorption through the oval and round window.[15,16,17]

Although Eisenman and Parisier[1] reported an interaural difference between the median BC 4000 Hz threshold of only 5 dB, we observed medians of 5 dB at 500 Hz, 1000 Hz, and 4000 Hz, but of 10 dB at 2000 Hz and 3000 Hz. Some authors argue that although these differences are statistically significant, they may not be clinically relevant. Notably however, the 5 dB and 10 dB differences referred to herein are medians, so in fact there were several patients in the study with greater degrees of impairment. We believe that understanding the sensorineural damage associated with cholesteatoma nowadays, where there are several kinds of prostheses and bone anchored hearing aids specifically indicated for patients with COM, is very valuable. This knowledge may assist the development or improvement of new technologies, and may be of even more benefit with regard to

BC than our demonstration that SNHL may be present in most patients with cholesteatoma, and that this damage can be clinically relevant in several cases.

Conclusion

The presence of cholesteatoma in the middle ear was associated with greater BC thresholds at all frequencies tested, when compared with the normal CLE. These BC differences were observed both in children and adults, and independently of cholesteatoma growth pattern.

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Cholesteatoma growth patterns: Are there audiometric differences between posterior epitympanic and posterior mesotympanic cholesteatoma?

Letícia Schmidt Rosito MD*, Fabio Andre Selaimen MD**, Luciana Silveira Netto*** , Sady Selaimen da Costa PhD****,

Hospital de Clinicas de Porto Alegre

ENT Department, Federal University of Rio Grande do Sul

*ENT, Otologist at Hospital de Clinicas de Porto Alegre (Corresponding author)

Av. Ramiro Barcelos 2350, Porto Alegre

Rio Grande do Sul 90035903, Brazil

Phone: 555196698796

E-mail: leticiarosito@gmail.com

**ENT resident at Hospital de Clinicas de Porto Alegre

*** Audiologist, researcher at Hospital de Clinicas de Porto Alegre

**** ENT Professor at Universidade Federal do Rio Grande do Sul

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Abstract

Objective: To verify whether the hearing impairment caused by posterior epitympanic differed from that caused by posterior mesotympanic cholesteatomas and to compare children and adults.

Study Design: Cross-sectional study.

Setting: Patients with cholesteatoma enrolled at a tertiary hospital between August 2000 and March 2013.

Patients: We evaluated 264 ears of patients with cholesteatoma, who had not been subjected to ear surgery.

Interventions: Otoendoscopy, pure-tone audiometry.

Main outcome measures: Route involved in cholesteatoma formation: posterior epitympanic or posterior mesotympanic. Air-bone gaps at 512 to 4,096 Hz and pure tone averages.

Results: The mean age of the patients enrolled in this study was 33.8 years, and 51.8% of them were male. Posterior epitympanic cholesteatoma was found in 50.4% of the study population. When the air–bone gaps were compared, the mesotympanic group had greater thresholds at 500 Hz, 2000 Hz, and a greater pure-tone average (P = 0.003, P = 0.03, and P = 0.02, respectively). While in adults the posterior mesotympanic had greater air-conduction and air-bone gap thresholds at several frequencies, no audiometric differences were found between posterior epitympanic and posterior mesotympanic cholesteatomas in children.

Conclusion: Posterior mesotympanic cholesteatoma showed greater air–bone gaps thresholds at the speech frequencies than posterior epitympanic cholesteatoma did. These differences were more evident in adults than in

children. Moreover, the two growth patterns were very similar with regard to all other audiometric parameters analyzed in this study.

INTRODUCTION

Acquired middle ear cholesteatoma is a destructive inflammatory disease, which predominantly arises either in the attic region (the pars flaccida of the tympanic membrane) or in the posterosuperior quadrant of the pars tensa. Ossicular destruction is one of the most frequent consequences of the progression of cholesteatoma, and the pattern and impact of this damage depends on its origin and the manner in which cholesteatoma develops. Partial or total ossicular defect is observed in approximately 80% of patients with cholesteatoma.[1]

The two main factors probably involved in cholesteatoma-related ossicular erosion are chronic inflammation, which leads to cytokine release and osteoclast activation, and pressure necrosis, caused by the cholesteatoma mass.[2] In a previous study,[3] we failed to show a correlation between the ossicular chain status, inflammatory histological degree, and thickness of the cholesteatoma perimatrix (indirect measurements of collagenases and inflammatory products, respectively). The pressure factor of the cholesteatoma on the ossicular chain, however, is more difficult to measure.

While the posterior epitympanic cholesteatoma arises primarily and destroys the malleus head and incus body, the posterior mesotympanic cholesteatoma develops on the fragile incus long process, erodes the incudostapedial joint, and may compromise the oval window niche more easily. These distinct growth patterns can lead to different hearing impairments, including sensorineural damage. Although a few studies have reported that the ossicular chain is intact in 26% of attical and in 10% of pars tensa cholesteatomas, most studies have failed to demonstrate audiometric differences between them.[3]

Therefore, the aims of this study were to investigate the differences in the hearing impairment caused by posterior epitympanic cholesteatomas and that caused by posterior mesotympanic cholesteatomas and to determine whether these differences are found both in children and in adults.

MATERIAL AND METHODS

This cross-sectional study included patients with chronic otitis media and a diagnosis of cholesteatoma at the Chronic Otitis Media Center of Hospital de Clinicas de Porto Alegre during the period between August 2000 and March 2013.

For all the patients, a detailed clinical history was obtained and otologic examination was performed. A careful and detailed cleaning of the ear canal was performed prior to the examination. In addition, fiberoptic otoendoscopy (0°, 4 mm Karl Storz endoscope) was performed in both the ears, and the results were recorded sequentially with clear patient identification.

The inclusion criterion was the presence of acquired cholesteatoma in at least one middle ear. The exclusion criteria included the following: history of any ear surgery except for tympanostomy for ventilation tube placement; impossibility of cleaning and videotoscopy for appropriate documentation; inability to define the diagnostic image, for example, due to polyps and inadequate cleaning of excess secretions; and congenital cholesteatoma, (anterior epitympanic), posterior epitympanic and mesotympanic (two routes), and indeterminate ones.

Next, we classified the cholesteatoma growth pattern into two groups:

1. Group 1: Posterior epitympanic -, when the cholesteatoma originated unequivocally and exclusively in the pars flaccida of the tympanic membrane;

2. Group 2: Posterior mesotympanic, when the cholesteatoma originated exclusively in the posterosuperior quadrant of the pars tensa of the tympanic membrane.

For comparison, patients were divided into a pediatric group, which comprised patients aged 0 to 18 years, 11 months, and 30 days (according to the United Nations Convention on the Rights of Children, 1989), and an adult group, in which patients were ≥19 years old.

All patients were subjected to pure-tone audiometry to determine air-conduction (AC) thresholds at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz, bone-conduction (BC) thresholds, and air–bone gaps (ABG) at 500, 1000, 2000, 3000, and 4000 Hz. The difference between the AC and BC thresholds was calculated to derive the ABG. In three cases, the ABG could not be calculated because of the absence of the AC and/or BC thresholds. Pure-tone audiometry was performed using the Interacoustic AD 27 audiometer with supraural TDH-39 earphones. For BC thresholds, a bone-conduction transmitter placed on the mastoid bone was used. For both AC and BC thresholds, narrow-band noise maskers were applied when needed. In young children, in whom it was challenging to obtain reliable measures of thresholds, playful conditioning (play-conditioned audiomety with supraural earphones) was applied. When necessary, two sessions of pure-tone audiometry were performed to confirm the results.

We analyzed the AC, BC, and ABG thresholds at each frequency. Pure-tone average (PTA) was calculated as the mean of the AC, BC, and ABG thresholds at 500, 1000, and 2000 Hz, which corresponds to the speech reception thresholds.

To quantify the degree of hearing loss, the AC PTA thresholds were stratified according to the WHO report (WHO/PDH/97.3, Geneva, 1997). The BC PTA was classified as ≤25 dB or >25 dB.

The hospital's Research Ethics Committee approved this study. Patients, or parents or guardians of all the children, signed a Free and Informed Consent form prior to inclusion in the study.

Statistical analysis was performed using IBM SPSS Statistics version 20. Qualitative variables were compared using the Chi-square test or Fisher's exact test. Patient age was compared using the Mann–Whitney test. Comparison of the AC thresholds at 250 Hz, 500 Hz, 1000 Hz, and AC PTA and comparison of the ABG at 500 Hz, 1000 Hz, and ABG PTA between the two groups and between children and adults were performed using the Student's t test. BC, AC, and ABG thresholds were compared using the nonparametric Mann–Whitney test. All tests were two-tailed, and the level of significance was set at $p < 0.05$.

RESULTS

A total of 264 ears met the selection criteria and were analyzed in this study. The age of the patients ranged from 4 to 82 years, and the mean age and standard deviation (SD) at the time of the first visit was 33.8 (19.0) years. Men constituted 51.8% of the study population, and 57.4% were adults. Patient distribution according to the cholesteatoma growth pattern was similar: 50.4% had posterior epitympanic cholesteatoma and 49.6% had posterior mesotympanic cholesteatoma.

When the two groups were compared, we observed a smaller prevalence of children and men in the posterior epitympanic cholesteatoma group. The

prevalence of BC PTA thresholds > 25 dB was low and similar between the two groups (Table 1).

	Posterior epitympanic cholesteatoma (n = 134)	Posterior mesotympanic cholesteatoma (n = 130)	p value
Age, median (interquartile range)	39 (21.7–52.0)	22.5 (14.0–45.7)	<0.001[a]
Children, no. (prevalence)	30 (22.4%)	58 (44.6%)	<0.001[b]
Male sex, no. (prevalence)	61 (45.5%)	78 (60.0%)	0.02[b]
Right ear, no. (prevalence)	68 (50.7%)	73 (50.0%)	0.90[b]
BC PTA, average (prevalence)			
Under or equal to 25 dB	104 (77.6%)	101 (77.7%)	1[b]
Over 25 dB	30 (22.4%)	29 (22.3%)	

[a] Mann–Whitney and [b]Fisher's exact test, BC PTA, bone-conduction pure-tone average

Table 1: *Description of the study population.*

According to the AC PTA, only 20% of the ears had normal hearing. The majority of them had at least moderate hearing loss. No difference was found between the pars flaccida and pars tensa cholesteatoma groups with regard the degree of hearing loss (P = 0.97, Figure 1).

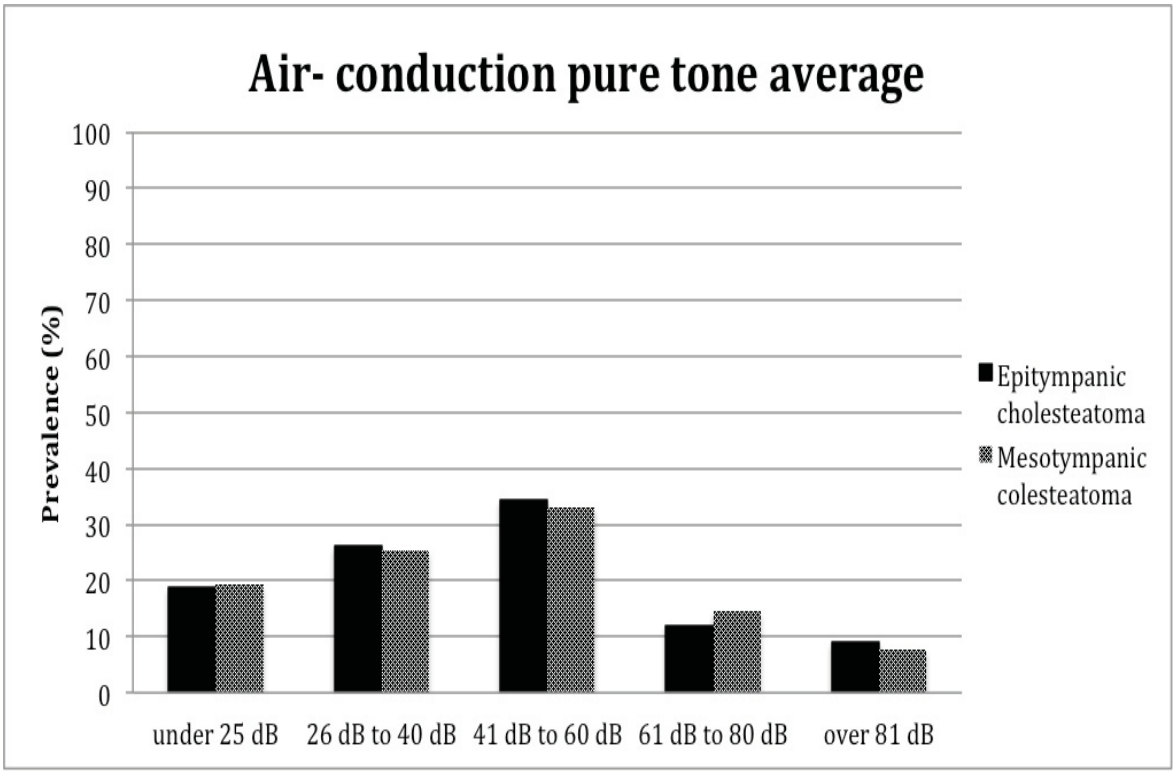
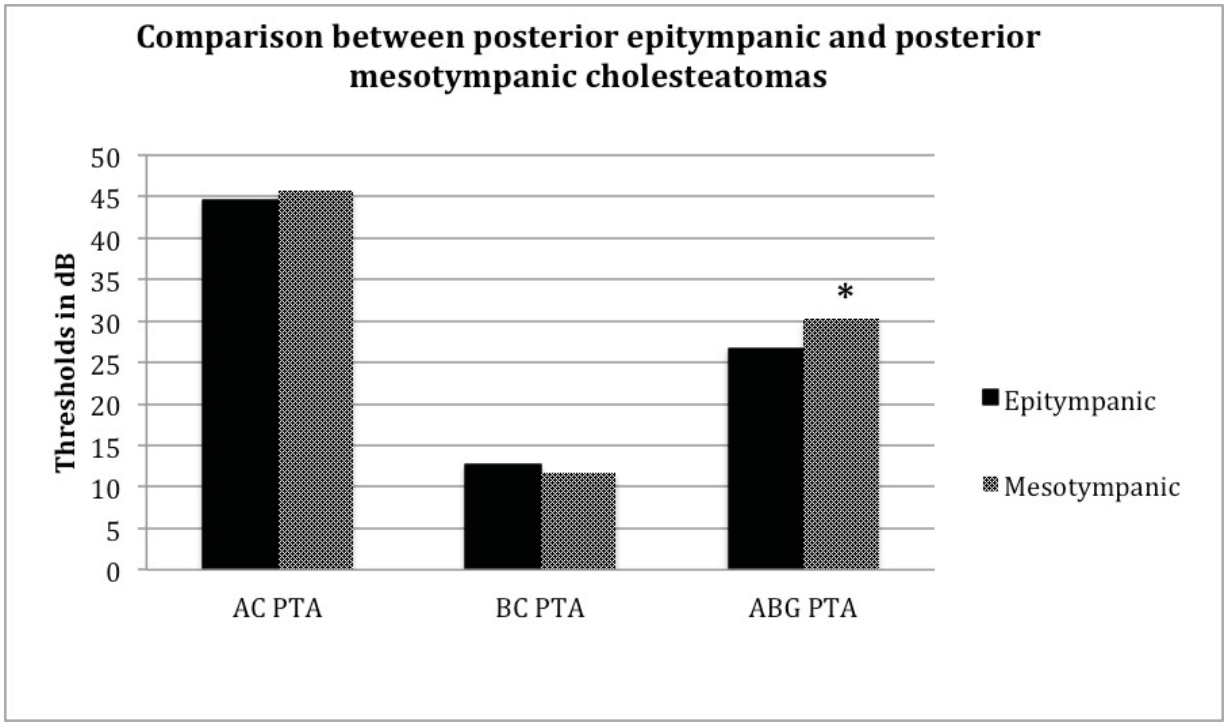


Figure 1: *Comparison of hearing loss degree between epitympanic and mesotympanic cholesteatomas.*

The means of the AC PTA and the medians of the BC PTA were similar between the pars flaccida and pars tensa cholesteatomas groups (p = 0.51 and p= 0.48, respectively). The results of ABG PTA, however, showed that the thresholds were greater in the posterior mesotympanic group (p= 0.026, Figure 2).



Means of AC PTA , air-conduction pure tone average; BC PTA, bone-conduction pure tone average; ABG PTA, air-bone gap pure tone average.

Figure 2: *Air-conduction, bone-conduction and air-bone gap PTAs comparison between epitympanic and mesotympanic cholesteatomas.*

Analysis of the children and adult groups showed that the AC PTA (Table 2) and BC PTA thresholds (Table 3) were similar between posterior epitympanic and posterior mesotympanic cholesteatomas. In adults, the mesotympanic cholesteatomas showed larger ABG PTA value, whereas, in children, no differences in ABG PTA were noted between the groups (Table 4).

AC Frequency	Posterior epitympanic cholesteatoma		Posterior mesotimpanic cholesteatoma		P value
	mean (SD)	median (ir)	mean (SD);	median (ir)	
250 Hz					
Children	40.0 (21.1);	37.5 (25.0–47.5)	42.1 (23.0);	40.0 (25.0–55.0)	0.670[a]
Adults	48.3 (19.1);	50.0 (35.0–60.0)	53.4 (18.1);	55.0 (40.0–65.0)	0.080[a]
500 Hz					
Children	38.8 (22.8);	35.0 (23.7–51.2)	41.8 (23.0);	37.5 (25.0–55.0)	0.56[a]
Adults	48.0 (19.3);	45.0 (35.0–60.0)	55.0 (18.2);	55.0 (40.0–65.0)	**0.016**[a]
1000 HZ					
Children	40.3 (24.3);	32.5 (25.0–55.0)	39.5 (23.5);	35.0 (23.7–50.0)	0.87[a]
Adults	47.9 (22.2);	45.0 (35.0–60.0)	55.4 (21.6);	55.0 (40.0–70.0)	**0.02**[a]
2000 Hz					
Children	32.3 (23.5);	30.0 (15.0–45.0)	33.7 (23.4);	30.0 (15.0–40.0)	0.83[b]
Adults	42.0 (23.4);	40.0 (25.0–55.0)	49.0 (21.6);	50.0 (30.0–65.0)	**0.004**[b]
3000 Hz					
Children	32.1 (23.4);	30.0 (15.0–40.0)	35.0 (23.1);	30.0 (20.0–40.0)	0.57[b]
Adults	47.4 (24.5);	45.0 (30.0–60.0)	49.0 (21.6);	50.0 (30.0–65.0)	**0.009**[b]
4000 Hz					
Children	35.8 (24.5);	30.0 (20.0–50.0)	35.9 (22.3);	30.0 (20.0–45.0)	0.94[b]
Adults	50.6 (24.9);	50.0 (35.0–65.0)	57.5 (21.7);	55.0 (40.0–75.0)	0.06[b]
6000 Hz					
Children	40.5 (24.3);	30.0 (22.5–52.5)	40.2 (22.9);	35.0 (25.0–50.0)	0.96[b]
Adults	59.2 (24.7);	55.0 (40.0–80.0)	61.5 (24.0);	57.6 (45.0–75.0)	0.62[b]
8000 Hz					
Children	39.0 (21.8);	35.0 (25.0–50.0)	38.0 (23.9);	35.0 (20.0–45.0)	0.57[b]
Adults	58.1 (27.6);	55.0 (35.0–77.5)	59.9 (26.5);	55.0 (35.0–80.0)	0.57[b]

[a] Student's t test for test independent samples
[b] Mann–Whitney test
AC, air-conduction threshold; AC PTA, air-conduction pure-tone average

Table 2: *Air- conduction thresholds comparison between posterior epitympanic and posterior mesotympanic cholestatomas in children and adults.*

BC Frequency	Posterior epitympanic cholesteatoma		Posterior mesotympanic cholesteatoma		P value [a]
	mean (SD);	median (ir)	mean (SD);	median (ir)	
500 Hz					
Children	07.5 (13.2);	05.0 (0.0–10.0)	07.9 (19.9);	05.0 (0.0–10.0)	0.42
Adults	18.9 (14.0);	15.0 (10.0–25.0)	18.9 (14.6);	15.0 (7.5–30.0)	0.92
1000 HZ					
Children	07.0 (13.8);	05.0 (0.0–6.2)	9.3 (19.9);	5.0 (0.0–10.0)	0.78
Adults	17.7 (16.7);	10.0 (5.0–25.0)	20.7 (16.4);	15.0 (10.0–23.5)	0.10
2000 Hz					
Children	10.8 (14.6);	10.0 (0.0–11.2)	12.3 (20.0);	10.0 (0.0–15.0)	0.88
Adults	23.0 (17.7);	20.0 (10.0–35.0)	25.6 (17.8);	20.0 (10.0–40.0)	0.27
3000 Hz					
Children	11.9 (14.0);	10.0 (5.0–15.0)	16.4 (19.3);	15.0 (10.0–15.0)	0.07
Adults	27.3 (19.6);	20.0 (10.0–45.0)	30.6 (17.4);	25.0 (15.0–45.0)	0.14
4000 Hz					
Children	13.5 (15.4);	10.0 (5.0–16.2)	15.7 (19.3);	12.5 (5.0–20.0)	0.38
Adults	27.4 (10.0);	20.0 (10.0–45.0)	30.9 (17.9);	27.5 (16.2–45.0)	0.09
BC PTA					
Children	08.5 (13.5);	04.2 (1.9–8.7)	07.0 (20.0);	05.8 (1.7–10.0)	0.64
Adults	20.0(15.5);	15.0 (9.2–27.5)	22.8 (16.0);	18.3(10.8–32.3)	0.15

[a]Mann–Whitney test
BC, bone-conduction threshold; BC PTA, bone-conduction pure-tone average

Table 3: *Bone- conduction thresholds comparison between posterior epitympanic and posterior mesotympanic cholestatomas in children and adults.*

ABG Frequency	Pars flaccida cholesteatoma		Pars tensa cholesteatoma		P value
	mean (SD); median (ir)		mean (SD); median (ir)		
500 Hz					
Children	30.7 (15.0);	30.0 (20.0–42.5)	34.2 (15.9);	35.0 (20.0–45.0)	0.33[a]
Adults	28.8 (14.2);	30.0 (20.0–40.0)	36.1 (15.69);	35.0 (25.0–47.5)	**0.002**[a]
1000 HZ					
Children	32.8 (17.4);	30.0 (20.0–52.5)	30.6 (14.4);	30.0 (20.0–45.0)	0.55[a]
Adults	29.8 (15.4);	30.0 (20.0–40.0)	34.6 (15.6);	35.0 (25.0–42.5)	**0.04**[a]
2000 Hz					
Children	20.5 (14.2);	20.0 (7.5–32.5)	21.3 (12.5);	20.0 (15.0–30.0)	0.76[b]
Adults	18.5 (13.6);	15.0 (10.0–30.0)	23.4 (12.8);	20.0 (15.0–32.5)	**0.012**[b]
3000 Hz					
Children	19.1 (14.5);	17.5 (5.0–33.7)	18.1 (12.1);	15.0 (10.0–25.0)	0.85[b]
Adults	19.4 (12.8);	20.0 (10.0–30.0)	25.1 (13.4);	25.0 (15.0–35.0)	**0.007**[b]
4000 Hz					
Children	21.4 (17.0);	15.0 (10.0–35.0)	20.0 (11.4);	20.0 (10.0–30.0)	0.89[b]
Adults	22.9 (14.4);	20.0 (10.0–35.0)	26.7 (14.0);	25.0 (15.0–35.0)	0.084[b]
ABG PTA					
Children	28.0 (14.5);	26.7 (19.2–41.7)	28.7 (12.9);	27 (18.3–38.3)	0.80[a]
Adults	25.7 (13.1);	26.7 (15.0–36.7)	31.4 (12.6);	30 (23.3–40.0)	**0.004**[a]

[a]Student's t test for test independent samples
[b]Mann–Whitney test
ABG, air–bone gap; ABG PTA, air–bone gap pure-tone average

Table 4: *Air-bone gap thresholds comparison between posterior epitympanic and posterior mesotympanic cholestatomas in children and adults.*

With regard to the audiometric frequencies in the entire study population, the BC thresholds of the pars flaccida cholesteatomas were greater only at 500 Hz (P = 0.032). No other differences between the groups were observed at the remaining frequencies (P = 0.48; Figure 3).

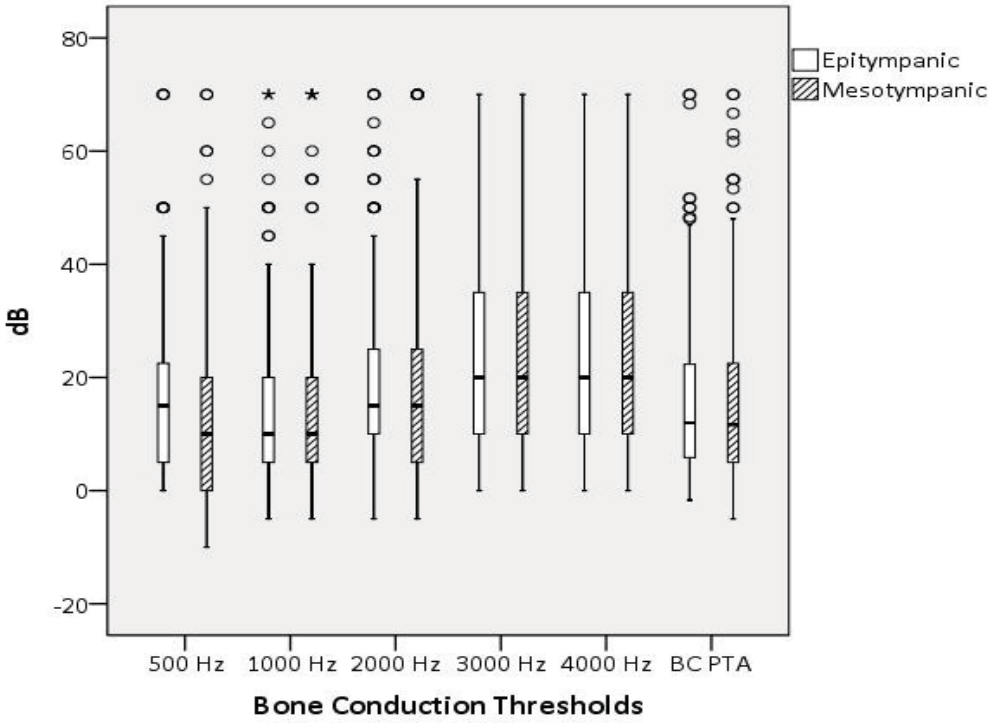


Figure 3: *Box-plot of bone-conduction thresholds in epitympanic and mesotympanic cholesteatomas. Median (black horizontal line inside the box), interquartile range (box superior limit (75th percentile)), and box inferior limit (25th percentile).*

A comparison of the median AC threshold for each frequency is shown in Figure 4.

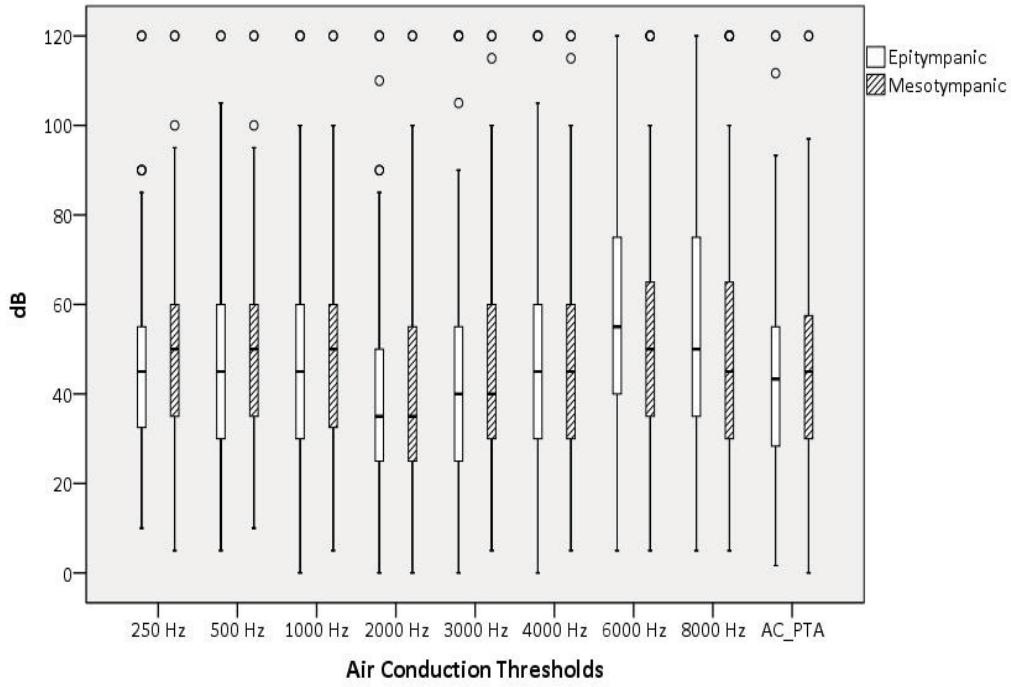


Figure 4: *Box-plot of air-conduction thresholds in epitympanic and mesotympanic cholesteatomas. Median (black horizontal line inside the box), interquartile range (box superior limit (75th percentile)), and box inferior limit (25th percentile).*

No differences were noted in the AC thresholds between the two groups at all the frequencies ($p > 0.05$). In posterior mesotympanic cholesteatoma group, however, larger ABG values were noted at 500 Hz and 2000 Hz ($p = 0.003$ and $p = 0.02$, respectively). No differences were found between the groups at all other frequencies (Figure 5).

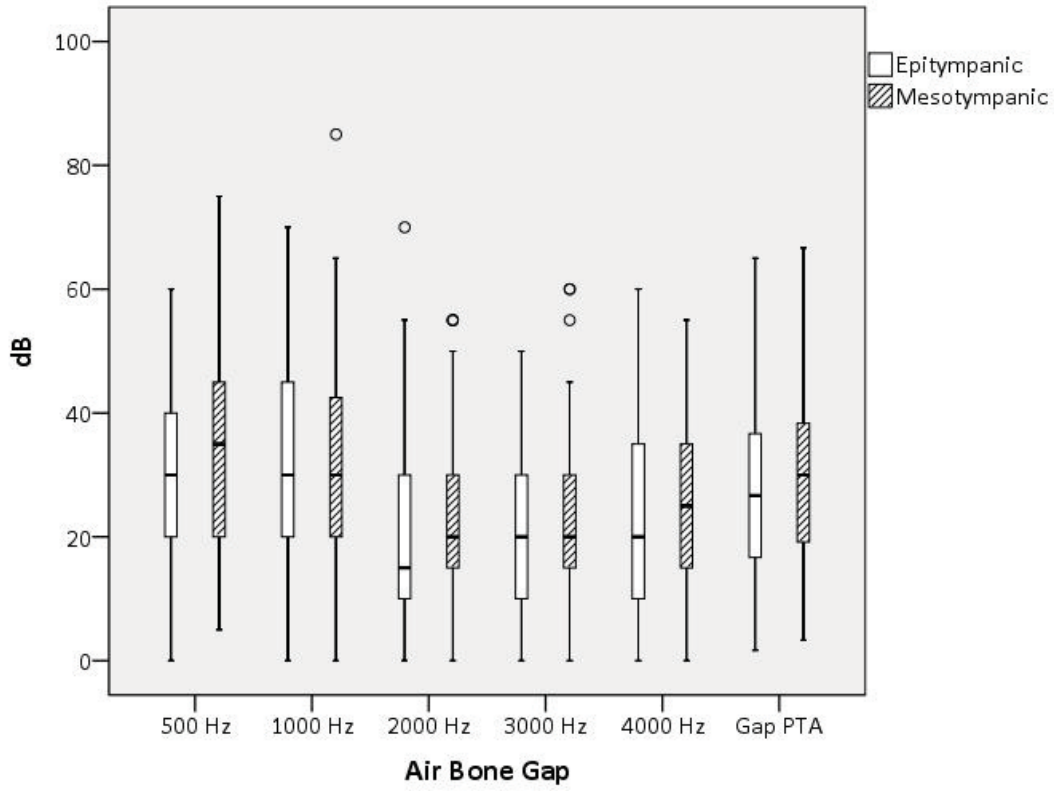


Figure 5: *Box-plot of air–bone conduction thresholds in epitympanic and mesotympanic cholesteatomas. Median (black horizontal line inside the box), interquartile range (box superior limit (75th percentile)), and box inferior limit (25th percentile).*

In adults, the posterior mesotympanic cholesteatomas group showed larger AC thresholds at 250 Hz, 500 Hz, 1000 Hz, and 2000 Hz, whereas, in children, no differences were found between the two groups (Table 2). With regard to the BC thresholds, no differences between the two groups were found in both the age groups (Table 3).

DISCUSSION

Chronic otitis media may lead to ossicular discontinuity. In a previous study, we concluded that children and teenagers with chronic otitis media with

cholesteatoma showed significantly greater ABG than those without cholesteatoma. Lower frequencies were more compromised than higher ones.[3]

It can be hypothesized that pars tensa cholesteatomas, which grow and evolve in the ossicular chain, may lead to greater hearing impairment than that due to pars flaccida cholesteatomas; however, previous studies have failed to verify this hypothesis. Our group found no significant differences between ABG associated with either cholesteatoma growth pattern when we examined 81 cholesteatoma patients under 18 years of age. The results of Durko's study (2004) were similar to those of our previous study, i.e., the average ABG values at 500 Hz to 4000 Hz were similar between the epitympanic and mesotympanic cholesteatomas.[4] These results can be attributed to three main factors: selection bias, sample size, and age of the study population.

In this study, patient selection was performed very carefully. Only those patients in whom the cholesteatoma localization was certain were included in this study. Dubious cases, other localizations, and indeterminate ones were systematically excluded. Furthermore, we included patients of all ages. In general, since cholesteatoma is a rare disease, it is challenging to perform studies with a large sample.

Although a few studies have found that, for cholesteatoma, the ABG is not a good predictor of ossicular chain discontinuity,[5,6,7] Martins et al., using a new and detailed scale to classify ossicular status, showed that the erosion of each ossicle contributes to the increase in ABG in a graded and independent manner.[10] Furthermore, several studies agree that the incus is the most affected ossicle.[2,8,9] This may be due to its incudal mass, its prominent bone marrow, and mainly, due to exposure and fragility of the long process. Martins et al. also showed that the

status of the incus has the most statistically significant association with ABG.[10] Maresh et al. compared primary and secondary acquired cholesteatomas (according to the authors, attical and mesotympanic cholesteatomas, respectively) and found that malleus erosion is more prevalent in the former and stapes erosion in the latter.[9] The prevalence of incus erosion did not differ between the groups. Indeed, we can infer that the localization of incus erosion differs between pars flaccida and pars tensa cholesteatomas.

Patients in posterior mesotympanic cholesteatoma group were younger than those in posterior epitympanic cholesteatoma group, probably because pars tensa cholesteatomas are more frequent in children than in adults. When we sorted the sample according to age, no significant audiometric differences between posterior epitympanic and posterior mesotympanic cholesteatomas were found in the pediatric group; the opposite phenomenon was noted in adults in which differences between the two groups were noted in several AC thresholds and at all ABG frequencies, except 4000 Hz. These distinctions may be explained by the aggressiveness of cholesteatoma and the evolution of the disease with time. Although this topic is still controversial, many studies suggest that cholesteatomas in children are more aggressive than those in adults[11]. The greater inflammatory activity and destruction power of cholesteatoma in this age group could be the reason for the similarity between posterior epitympanic cholesteatomas and posterior mesotympanic cholesteatoma. On the other hand, in adults, cholesteatomas have probably evolved for a longer duration. Sade and Fuchs (1994), however, found that, although the destruction percentage in the stapes and malleus was similar in children and adults, the incus was exposed to significantly higher destruction in adults.[12] Furthermore, the absence of a

difference in cholesteatoma growth patterns in children may be attributed to the small statistical power of the study—the sample size was reduced when the study population was divided into adults and children.

We must consider, however, that the ABG differences between pars flaccida and pars tensa cholesteatomas could be underestimated in our study. Because of the well-known collumelar effect of the cholesteatoma (i.e., according to its position in relation to the oval niche, it can amplify and transmit sound into the inner ear), the ABG in the posterior mesotympanic cholesteatomas could be smaller in some cases, and thus, even more similar to the ABG in the pars flaccida cholesteatomas, in which this effect is less pronounced. This phenomenon could also contribute to the dissociation between ossicular chain damage and the ABG, because very advanced cholesteatomas, with complete erosion of the supra structure of the incus and stapes, could propagate the sonorous wave effectively.

Although there are important differences in the growth pattern between epitympanic and mesotympanic cholesteatomas, especially in terms of their propagation and type of ossicular destruction, we believe that with the progression of the disease and greater bony erosion, these two groups could became more similar. We argue, however, that this bias was, at least partially prevented by our rigid selection criteria, which excluded the more advanced or extensive cases.

An understanding of the different types, behavioral patterns, and hearing impairment caused by cholesteatomas will enable us to improve the prognosis of this disease by optimizing its treatment and improving surgical techniques for both

complete removal of the pathological tissue and successful reconstruction of the damaged ossicles.

In conclusion, compared with posterior epitympanic cholesteatomas, posterior mesotympanic cholesteatomas had greater ABG thresholds at 500 Hz, 2000 Hz, and ABG PTA, which correspond to the speech reception frequencies. The two growth patterns, however, were very similar with regard to the other audiometric parameters. In children, no audiometric differences were found between the two groups, whereas, in adults, compared with posterior epitympanic cholesteatomas, posterior mesotympanic cholesteatomas showed higher ABG thresholds at 500 Hz to 3000 Hz and higher ABG PTA, in addition to higher AC thresholds at several frequencies.

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The contralateral ear in cholesteatoma

**Short running head: Contralateral ear in cholesteatoma

Letícia Schmidt Rosito, MD*; Sady Selaimen da Costa, PhD;

Department of Otolaryngology - Head and Neck Surgery, Hospital de Clinicas de Porto Alegre,
Department of Otolaryngology - Head and Neck Surgery , Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil.

*Correspondence and reprint requests author: Letícia Schmidt Rosito, Department of Otolaryngology - Head and Neck Surgery. Hospital de Clinicas de Porto Alegre, Av. Ramiro Barcelos 2350, Porto Alegre, Rio Grande do Sul, CEP 90035-903, Brasil zipcode 90035903.

Phone: 55-51-96-69-8796;

E-mail: leticiarosito@gmail.com

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ABSTRACT

Objective: Middle ear cholesteatoma has been extensively studied. Theories of cholesteatoma pathogenesis involving previous tympanic membrane retraction are the most widely accepted, but the contralateral ear in patients with cholesteatoma remains unstudied. This study aimed to investigate the contralateral ear in patients with cholesteatoma, and to determine whether the characteristics of it differ according to patient age and cholesteatoma growth patterns.

Study Design: This study was cross sectional

Methods: We evaluated 356 patients with middle ear cholesteatoma in at least one ear, and no history of surgery, between August 2000 and March 2013. Otoendoscopy was conducted on both the affected and the contralateral ear. They were classified as normal, tympanic membrane perforation, moderate to severe tympanic membrane retraction and cholesteatoma

Results: The mean age of the patients was 32.77 years, and 53.1% of the cohort were female. Only 34.8% of the contralateral ears were normal. The most common abnormality was moderate to severe tympanic membrane retraction (41.6%). Cholesteatoma was identified in 16%. Children exhibited a greater frequency of tympanic membrane retractions, whereas adults exhibited a greater frequency of cholesteatoma. All of the contralateral ears in the anterior epitympanic group were normal, but otherwise there were no differences in the contralateral ear when we compared the cholesteatoma growth patterns.

Conclusion: Patients diagnosed with acquired cholesteatoma of one ear are significantly more likely to exhibit abnormalities of the contralateral ear.

Keywords: Cholesteatoma, tympanic membrane retraction, growth pattern, contralateral ear

Level of Evidence: 4

INTRODUCTION

One of the hypotheses for the pathogenesis of chronic otitis media (COM) is the continuum theory in wich Paparella et al postulate that otitis media exists through a continuous series of events[1]. After an initial triggering factor, and in the absence of arresting mechanisms, a serous or purulent otitis may become seromucoid, mucoid, and finally chronic. This theory suggests that the earlier phases of otitis media may progress over time into more advanced pathologies such as granulation tissue, cholesterol granuloma and cholesteatoma[1]. Several animals[2-4] and histopathogical[1,5] studies have been demonstrated the continuum, but clinical studies with a long follow up are very difficult to perform. As otitis media with effusion has been reported as bilateral in 54% to 76% of the cases[6,7], it is logical to imagine that, in the absence of spontaneous resolution, the pathology may progress bilaterally in a considerable proportion of the cases, although with differing degrees of severity. So, the analysis of the contralateral ear (CLE) in patients with COM can be a viable form to study in humans, although indirectly, the disease's pathogenesis

Although the first study of the CLE in patients with COM was performed in 1984[8], few have been published until now. Our group has been studying the CLE in patients with COM since 2008.[9] Our clinical, histological, radiological and functional findings have systematically demonstrated a high frequency of alterations in the CLE.[9-12] and an asymmetry between the two ears.

This study aimed to describe the CLE now only in patients with COM with cholesteatoma, and investigate potential differences according to patient age and cholesteatoma growth patterns.

MATERIALS AND METHODS

We studied 356 consecutive patients with middle ear cholesteatoma, treated at a tertiary hospital from August 2000 to March 2013. A detailed clinical history and otologic examination were completed for each patient. Careful and thorough cleaning of the ear canal was performed prior to the examination. Fiber optic otoendoscopy of 0° and 4 mm (Karl Storz) in both ears was recorded sequentially with Cyberlink Powerdirector (version 7, 2008).

The inclusion criterion was the presence of cholesteatoma in at least one middle ear. The exclusion criteria included refusal to participate in the study, history of any ear surgery except for tympanostomy for ventilation tube placement, and impossibility of cleaning and videotoscopy for appropriate documentation. The recorded images were independently reviewed, and then blinded such that changes in the contralateral ear (CLE) were described without knowledge of the main ear (ME) findings. We used specific protocols in a systematic manner, in accordance with the descriptions below, and each was conducted by the same researcher.

All ears were reviewed using digital videotoscopy, and separated into ME and CLE. The ME was defined as either that with cholesteatoma, or that which was more symptomatic. Next we classified the cholesteatoma growth pattern, using methodology modified from that described by Jackler:[13]

1. Anterior epitympanic - originating cranially and anteriorly to the malleus head.

2. Posterior epitympanic - originating in the pars flaccida (PF).

3. Posterior mesotympanic - arising in the posterosuperior quadrant of the pars tensa (PT).

4. Posterior epitympanic and mesotympanic (two routes) - involvement of the PF and PT (dual origin of cholesteatoma).

5. Undetermined - the precise growth pattern could not be determined from the videoscopy.

"Normal" ears on videotoscopy were defined as those that were unchanged, or exhibited only minor changes such as neotympanum, tympanosclerosis, mild retraction, or effusion. Perforation of the tympanic membrane (TM), moderate or severe retraction (stages of Sadé II, III and IV[14]), and cholesteatoma were considered significant changes. For comparison, patients were divided into a pediatric group, which comprised patients aged 0 to 18 years, 11 months, and 30 days (according to the United Nations Convention on the Rights of Children, 1989), and an adult group, consisting of patients aged ≥19 years.

The scientific and ethical content of this work was approved by our institution’s Group Research and Graduate Studies Department (protocol number 14920). All the study participants authorized the use of their anonymous data in the study. Statistical analysis was performed via the Chi-square test and Fisher's exact test, which were conducted using SPSS (version 20) statistics software. Statistical significance was set at $p < 0.05$.

RESULTS

The mean patient age was 32.77 years (SD 19.92, range 4–82), 128 (36.2%) were children, and 189 (53.1%) were female. The frequencies of the different cholesteatoma growth patterns in the ME are shown in Table 1.

Cholesteatoma in the main ear	Frequency	Percentage
Anterior epitympanic	7	2.0%
Posterior epitympanic	120	33.7%
Posterior mesotympanic	122	34.3%
Two routes	51	14.3%
Indeterminate	56	15.7%

Table 1: *Classification of main ear cholesteatoma growth pattern*

Only 124 (34.8%) of the CLE were normal. The main changes in the CLE are shown in Table 2.

Observed CLE changes	Frequency (%)
Tympanic membrane perforation	24 (6.7%)
Moderate or severe tympanic membrane retraction	148 (41.6%)
Cholesteatoma	60 (16.9%)
Normal	124 (34.8%)

Table 2: *Significant changes observed in the contralateral ear (CLE)*

There were no significant differences between adults and children with regard to the frequencies of CLE alterations (64.3% vs. 65.6%, *p* = 0.818). There was however, a significantly higher frequency of TM retraction in the CLE in children, and a higher frequency of cholesteatoma in adults (*p* = 0.025) (Figure 1).

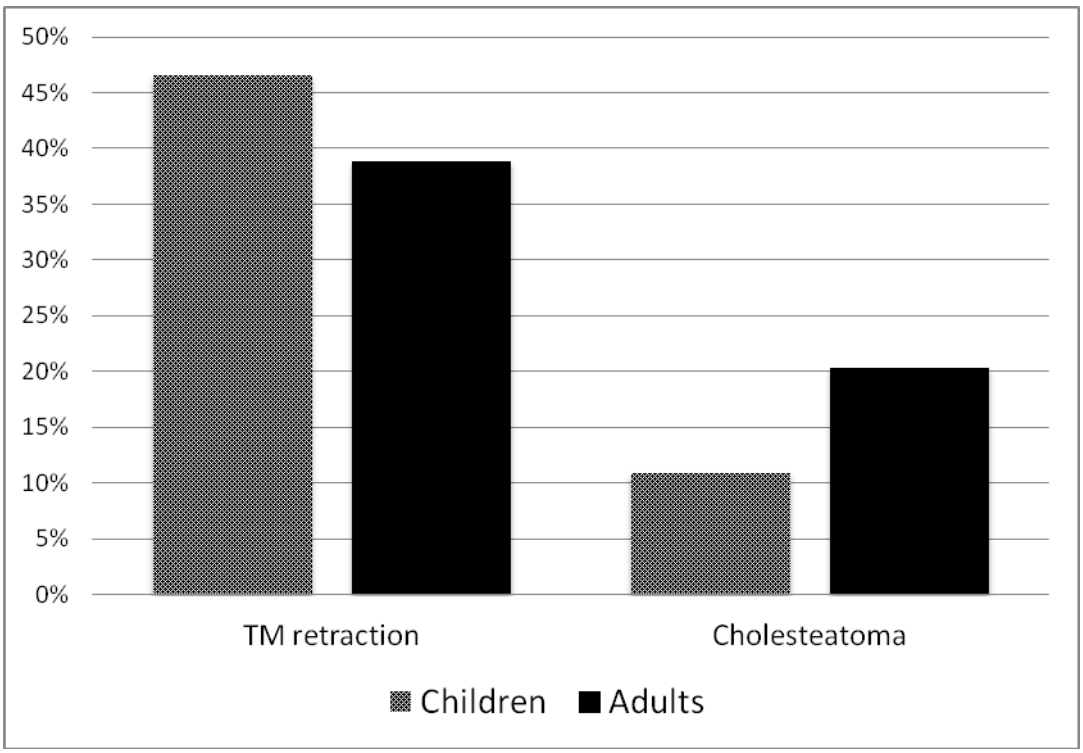

Figure 1: *Cholesteatoma and tympanic membrane retraction frequency in the contralateral ear, and comparison between children and adults.*

With regard to cholesteatoma growth pattern, there was no significant difference in the frequencies of alterations in the CLE (*p* = 0.185) (Figure 2).

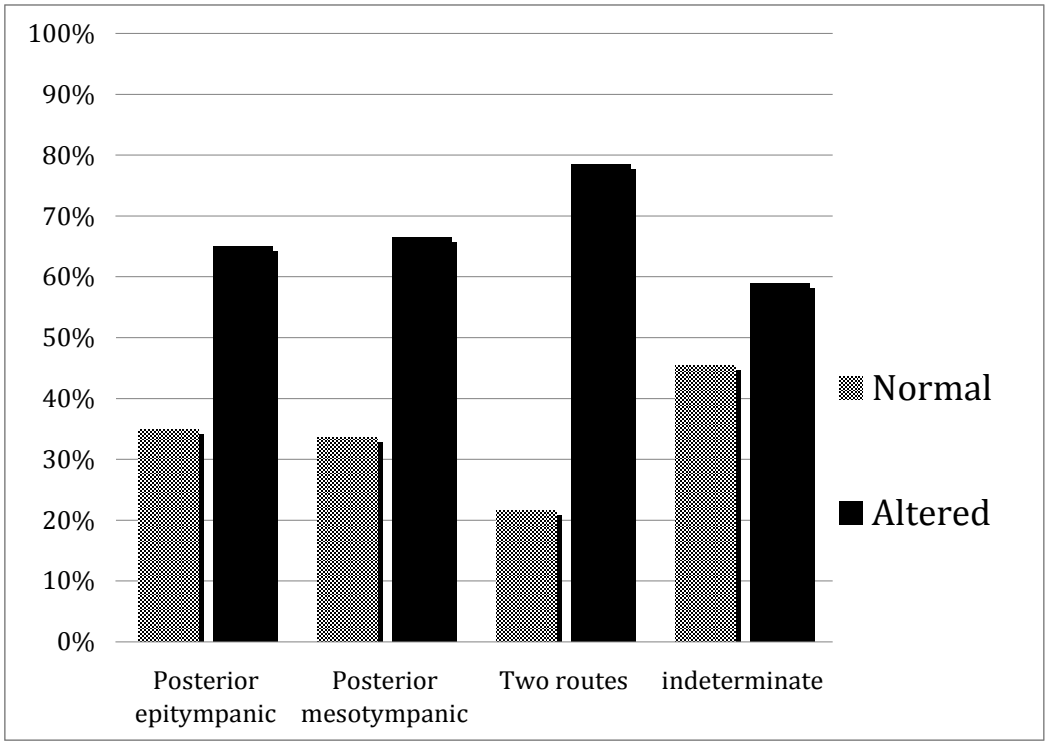

Figure 2: *Frequency of alterations in the contralateral ear among the different cholesteatoma growth patterns in the main ear.*

In the anterior epitympanic cholesteatoma group, however, all CLEs were normal. As the anterior epitympanic group was very small (only 7 patients), it was excluded from the statistical analysis. With regard to comparison of the alterations in the CLE among the different cholesteatoma growth pattern groups, there was no statistically significant difference (p = 0.329), as shown in Figure 3.

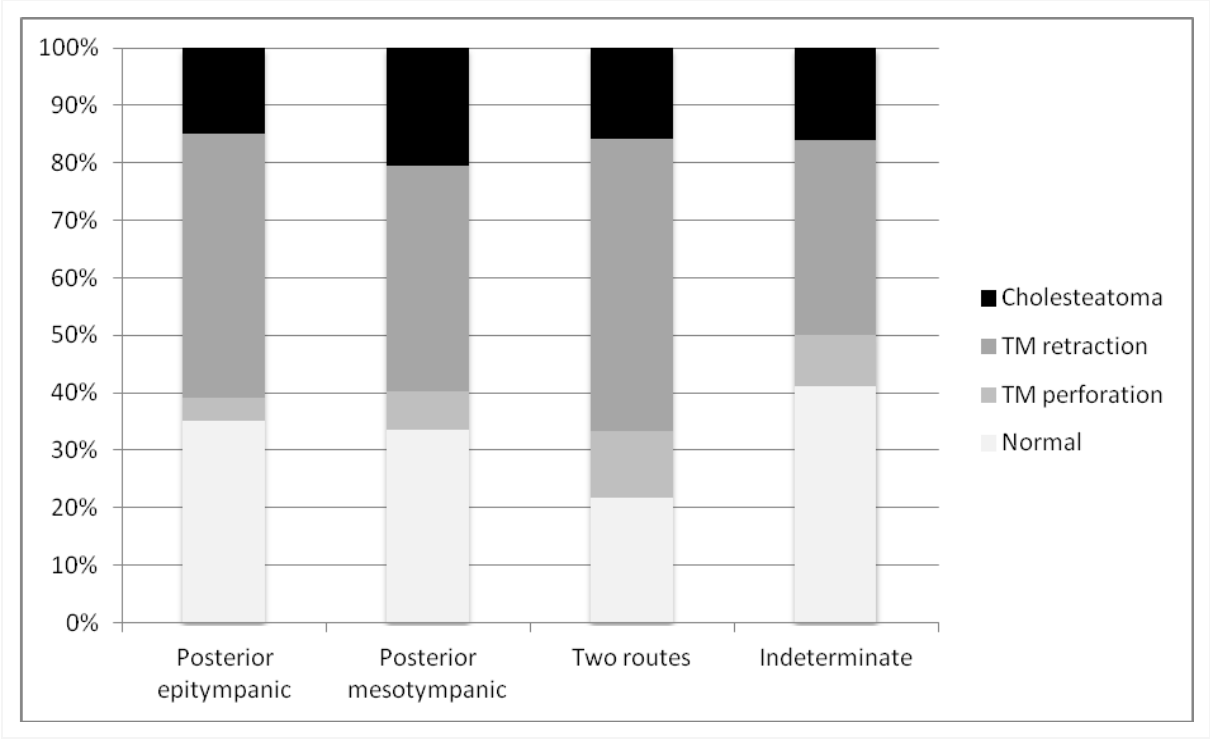

Figure 3: *Alterations in the contralateral ear among the cholesteatoma growth patterns in the main ear.*

DISCUSSION

Chalton and Sterns[8] performed the first study of the CLE in patients with COM, in 1984. They found abnormalities in 53.4% of the CLEs in patients with cholesteatoma in the ME, and TM retraction was the most prevalent alteration. Vartiainen at al.[15] found some degree of abnormality in 63% of the CLEs of patients with COM, and again, TM retraction was the most frequent finding.

In our previous study[9] performed in 2008, which included patients with COM both with and without cholesteatoma, we detected significant changes in 55.8% of the CLEs, including TM perforations, moderate and severe TM retractions, granulation tissue, and cholesteatoma. The most frequent alteration observed in

the CLE was TM retraction. Interestingly, patients with cholesteatoma had a greater frequency of alterations in the CLE. In our previous histological study,[10] as we expected, we found an even higher frequency of CLE alterations: 91.8%, with 78.0% being significant changes. Granulation tissue was the most frequent observation. In that study however, there was not a significant difference between COM with and without cholesteatoma, but a strong direct correlation was observed between the extent of cholesteatoma in the more damaged ear, and the CLE.

In the present study, we detected a frequency of significant changes in the CLE of 65.2%, moderate and severe retractions of the TM being the most frequent. These findings are in general agreement with previous studies of COM[8,15]. The presence of cholesteatoma was observed in both ears in 16.9% of patients. The frequency of CLE alterations in children and adults was similar. It is important to note however, that children exhibited greater frequencies of moderate and severe TM retractions in the CLE, while adults exhibited a greater frequency of cholesteatoma. These findings suggest that: (1) TM retraction seems to be the main route to cholesteatoma formation, and (2) once there is no difference in the frequency of normality of the CLE between children and adults, the involvement of the CLE seems to be an early feature in all patients with ME cholesteatoma. A possible explanation for this is that theoretically, adults have had the disease for longer than children, and the earlier phases of the disease could manifest during childhood. Critically analyzing the timeline of the events involved in the pathogenesis of the disease, it seems logical that we found the causes (TM retractions) to be more prevalent in children, while the consequences (cholesteatoma) were more common in adults.

Summarizing, when the most affected ear is already in the final stages of the continuum, in 66% the CLE is cursing to the same direction only one or two steps behind. Certainly, TM retraction is an important, possibly crucial step in this process. This situation represents what Costa et al.[10] referred to as “the crystal ball effect”, because frequently the most affected ear can predict the future status of the CLE.[3]

Using videotoscopy, we can now clearly identify the various types of cholesteatoma growth patterns. Although they differ in their formation and propagation routes,[13,16,17] the alterations in the CLE were very similar among the groups. In the anterior epitympanic group, however, all the CLEs were normal. This finding suggests that anterior epitympanic cholesteatoma may be congenital, while all other cholesteatoma growth patterns are acquired, and originate principally from retractions of the pars flaccida, pars tensa or both.

We believe that the CLE findings in patients with cholesteatoma are valuable in two fundamental respects: (1) They enhance understanding of the pathogenesis of the condition, and (2) they provide insight that may be useful in the contexts of treatment, follow-up, and counseling. Thus, the CLE should always be examined in detail and monitored over time, especially in patients with ME cholesteatoma, with the goal of early diagnosis of alterations. Further, if necessary, therapeutic action at the most opportune time should be undertaken, before the severe functional and anatomical damage characteristic of cholesteatoma becomes established.

CONCLUSION

Patients with acquired cholesteatoma have a greater probability of having significant alterations in the CLE. The frequencies of alterations were generally similar in adults and children, although children had more TM retraction and adults more cholesteatoma, in the CLE. The frequencies of CLE alterations and the types of these alterations were similar between the several cholesteatoma growth patterns.

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Localization of tympanic membrane retraction and acquired cholesteatoma in the contralateral ear: Searching for cholesteatoma growth patterns

Short running head: Cholesteatoma growth patterns

Letícia Schmidt Rosito, MD*; Sady Selaimen da Costa, PhD;

Department of Otolaryngology - Head and Neck Surgery, Hospital de Clinicas de Porto Alegre,
Department of Otolaryngology - Head and Neck Surgery, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil.

*Correspondence and reprint requests author: Letícia Schmidt Rosito, Department of Otolaryngology - Head and Neck Surgery. Hospital de Clinicas de Porto Alegre, Av. Ramiro Barcelos 2350, Porto Alegre, Rio Grande do Sul, CEP 90035-903, Brasil zipcode 90035903.

Phone: 55-51-96-69-8796;

E-mail: leticiarosito@gmail.com

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ABSTRACT

Objective: Investigate the cholesteatoma growth pattern and location of tympanic membrane retraction in the contralateral ear of patients with acquired middle ear cholesteatoma who were treated for chronic otitis media.

Study design: Cross-sectional study.

Setting: Tertiary hospital.

Patients: Consecutive patients (*N* = 242) treated for chronic otitis media, diagnosed with posterior epitympanic (49.6%) or mesotympanic cholesteatoma in at least one ear between August 2000 and March 2013, and no surgical history (mean [SD] age, 33.35 [19.45] years; 51.7% women and 65.3% adults).

Intervention: Videotoscopy of both ears.

Main outcome measures: Prevalences of posterior epitympanic and mesotympanic cholesteatoma and moderate-to-severe pars tensa and flaccida retraction in the contralateral ear.

Results: Cholesteatoma and tympanic membrane retraction were identified in 17.8% and 42.6% of the contralateral ears, respectively. When the primary ears had posterior epitympanic or mesotympanic cholesteatoma, the same cholesteatoma growth pattern was present in 89.5% and 64% of the contralateral ears, respectively ($p < 0.0001$). A similar phenomenon was observed in cases of pars tensa and flaccida retraction ($p < 0.0001$).

Conclusion: Patients with acquired middle ear cholesteatoma are very likely to have the same cholesteatoma growth pattern and location of tympanic membrane retraction in the contralateral ear. Chronic otitis media with acquired middle ear cholesteatoma seems to be a constitutional process with a high prevalence of bilaterality.

Keywords: cholesteatoma, middle ear; tympanic membrane; otitis media; endoscopy

INTRODUCTION

Although a few centuries have passed since its first description by Duverney, in 1689 (1), the pathogenesis of acquired middle ear cholesteatoma is still controversial. At present, the four main theories on its pathogenesis are as follows: metaplasia, based on transformation of the inflamed middle ear epithelium into keratinized squamous epithelium; migration, based on ingrowth of the squamous epithelium through a pre-existing peripheral perforation; invagination, based on retraction of the pars tensa or flaccida due to chronic dysfunction of the eustachian tube; and papillary proliferation, based on infection leading to proliferation of epithelial cones in the basal layers of the pars tensa or flaccida (2). These theories mainly originated from clinical observations and experimental studies (3) since well-designed cohorts are difficult to perform because cholesteatoma is an infrequent disease and needs several years to develop.

Since 2008, we have been indirectly studying the pathogenesis of chronic otitis media by examining the contralateral ear (CLE) (4). Ours observations have systematically showed a high prevalence of alterations in the CLE in clinical (4), histopathological (5), radiological (6) and functional (7) studies. Moreover, our results demonstrated that the frequency of alterations in the CLE was even higher in patients with COM with cholesteatoma (4). Tympanic membrane retraction and cholesteatoma in the contralateral ear tended to be common in the patients with cholesteatoma, regardless of the growth pattern (unpublished data). In this cross-sectional study, we aim to study the CLE of with cholesteatoma focusing the presence of tympanic membrane retraction and cholesteatoma. We aim to investigate the cholesteatoma growth pattern and location of tympanic membrane

retraction in CLE of patients with acquired middle ear cholesteatoma who were treated for chronic otitis media.

MATERIALS AND METHODS

The study included 242 consecutive outpatients who were treated for chronic otitis media between August 2000 and March 2013. It was approved by the hospital's Group Research and Graduate Studies Department (protocol number 14920) and was performed in accordance with the Helsinki Declaration. All the subjects consented in writing to the use of their anonymous data.

Their detailed clinical history was recorded, and both the ears were examined with a fiber-optic otoendoscope (0° and 4 mm; Karl *Storz GmbH,* Tuttlingen, Germany) after carefully cleaning the ear canals. The images were clearly identified and recorded with PowerDirector version 7 (CyberLink Corporation, Taipei, Taiwan). They were then independently reviewed and blinded, so changes in the contralateral ear were described without knowledge of the growth pattern in the primary ear.

The inclusion criterion was presence of either posterior epitympanic or posterior mesotympanic cholesteatoma in at least one middle ear. Patients were excluded if they had a history of any ear surgery except tympanostomy for ventilation tube placement, congenital cholesteatoma, anterior epitympanic cholesteatoma, both posterior epitympanic and mesotympanic cholesteatomas, or an undetermined cholesteatoma growth pattern.

For data analysis, the primary ears were defined as either having acquired cholesteatoma or being symptomatic. We classified the cholesteatoma growth pattern on the basis of a modification of Jackler (8):

1. Posterior epitympanic or attic: originating exclusively from the pars flaccida;

2. Posterior mesotympanic or tensa: arising from the posterosuperior quadrant of the pars tensa;

3. Anterior epitympanic: originating before the malleus head;

4. Both posterior epitympanic and mesotympanic: involving both the pars flaccida and tensa;

5. Undetermined: the precise growth pattern could not be identified by videotoscopy.

Contralateral ears were classified according to the following criteria : showing no changes or having only minor changes, such as neotympanum, tympanosclerosis, mild retraction, and effusion, were considered normal. Tympanic membrane perforation, moderate or severe retraction, and cholesteatoma were considered significant changes. Tympanic membrane retraction was classified by location and severity according to a modification of Sadé (Table 1) (9).

Location	Grade	Definition
Pars tensa	Slight	Retraction only
	Moderate	Touches the icudostapedial articulation
	Severe	Touches the promontory or ossicular erosion
Pars flaccida	Slight	Retraction only
	Moderate	Touches the malleus head
	Severe	Ossicular erosion

TABLE 1. *Classification of tympanic membrane retraction*

When retraction of both the pars flaccida and the pars tensa was observed, the location of the more severe change was considered to classify the cases of tympanic membrane retraction into only two groups: (i) retraction of the pars flaccida or both the pars flaccida (more severe) and the pars tensa, and (ii) retraction of the pars tensa or both the pars tensa (more severe) and the pars flaccida.

Statistical analysis was performed by using chi-square and Fisher's exact test in SPSS software (SPSS, Chicago, IL). All tests were two-sided. Statistical significance was set at $p \leq 0.05$.

RESULTS

The mean (SD) patient age was 33.35 (19.45) years (range, 4–82 years) and 125 patients (51.7%) were women. Cholesteatoma was initially diagnosed in the right ears of 125 (51.7%) patients. In particular, posterior mesotympanic and epitympanic cholesteatomas were present in the primary ears of 122 (50.4%) and 120 (49.6%) patients, respectively.

Only 83 (34.3%) contralateral ears were considered normal. Tympanic membrane retraction was the most common significant change (103 contralateral ears, 42.6%). Cholesteatoma was observed in 43 (17.8%) contralateral ears.

Analyzing only the 103 patients with moderate and severe tympanic membrane retraction in the contralateral ear, we observed that when the primary ear presented posterior epitympanic cholesteatoma, the contralateral ear had pars flaccida retraction in 72.7% of the cases and both pars flaccida and tensa retraction in 25.5% of the cases. When posterior mesotympanic cholesteatoma was present in the primary ears, 41.7% and 39.6% of the contralateral ears had

pars tensa retraction and both pars flaccida and tensa retraction, respectively (p < 0.0001) (Fig. 1).

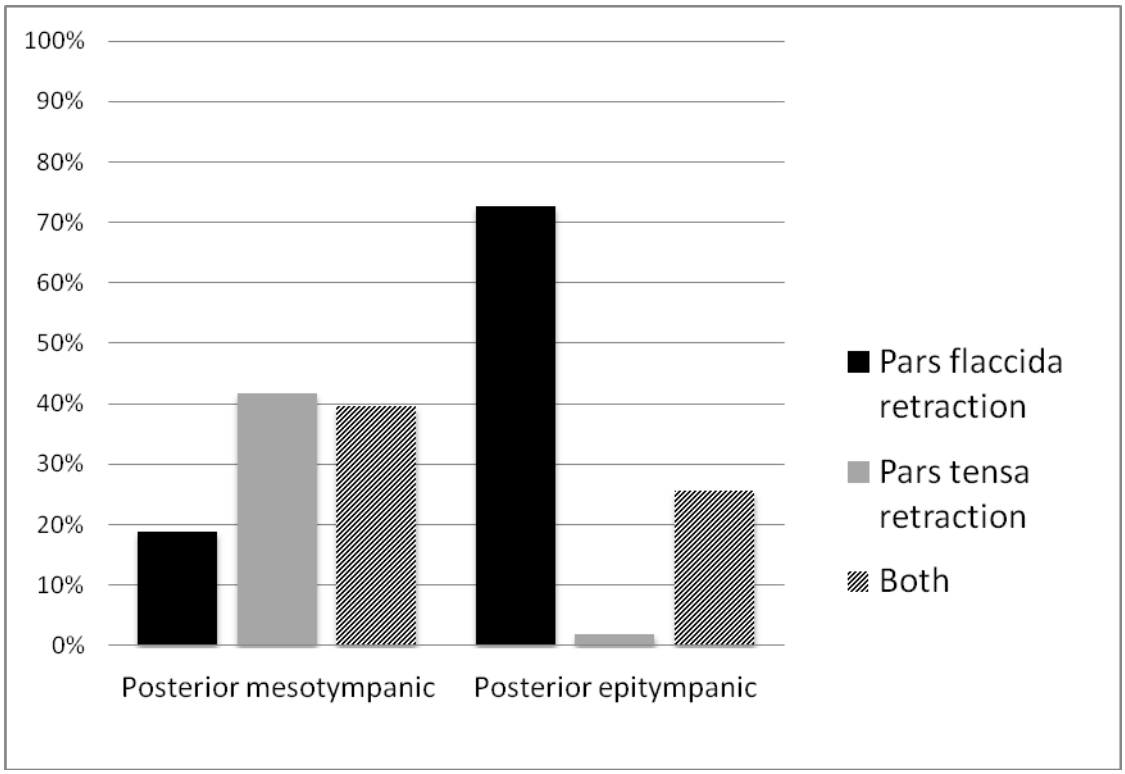

FIG. 1. *Overall prevalence of tympanic membrane retraction in the contralateral ear according to the cholesteatoma growth pattern in the primary ear.*

When tympanic membrane retraction was analyzed according to the two groups, it was found to occur at the same region in the contralateral ear as the cholesteatoma in the primary ear (p < 0.0001) (Fig. 2).

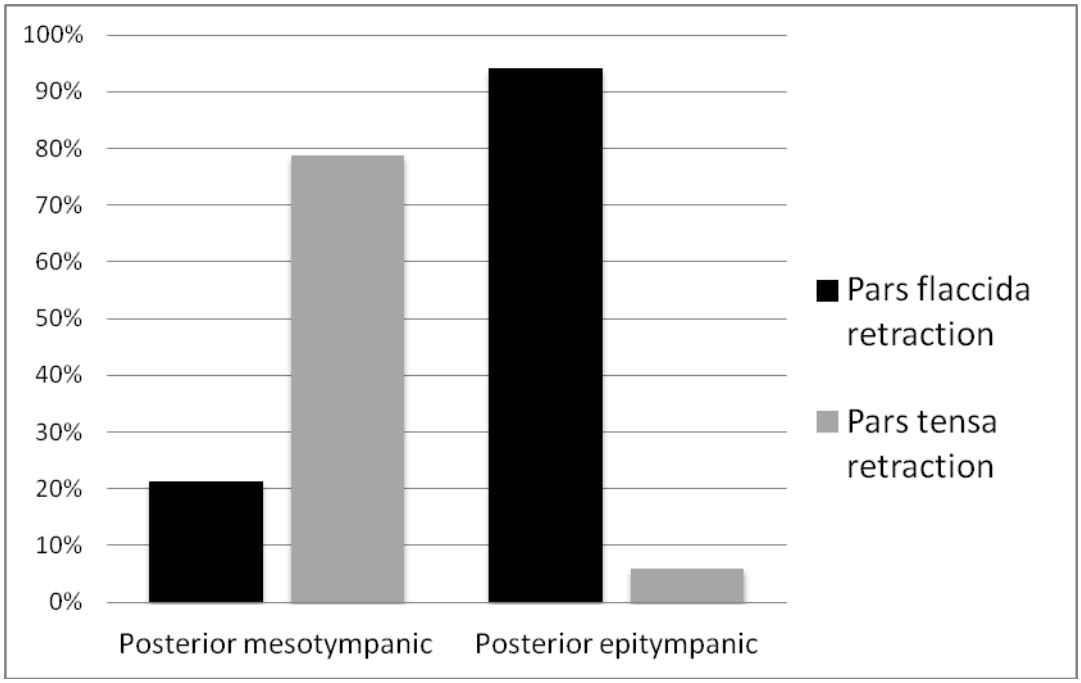

FIG. 2. *Prevalence of pars flaccida and tensa retraction in the contralateral ear according to the cholesteatoma growth pattern in the primary ear.*

In bilateral cases of cholesteatoma, 89.5% of the contralateral ears had attic cholesteatomas when posterior epitympanic cholesteatoma was present in the primary ears. Further, when posterior mesotympanic cholesteatoma was observed in the primary ears, the same growth pattern was observed in 64% of the contralateral ears ($p < 0.0001$) (Fig. 3).

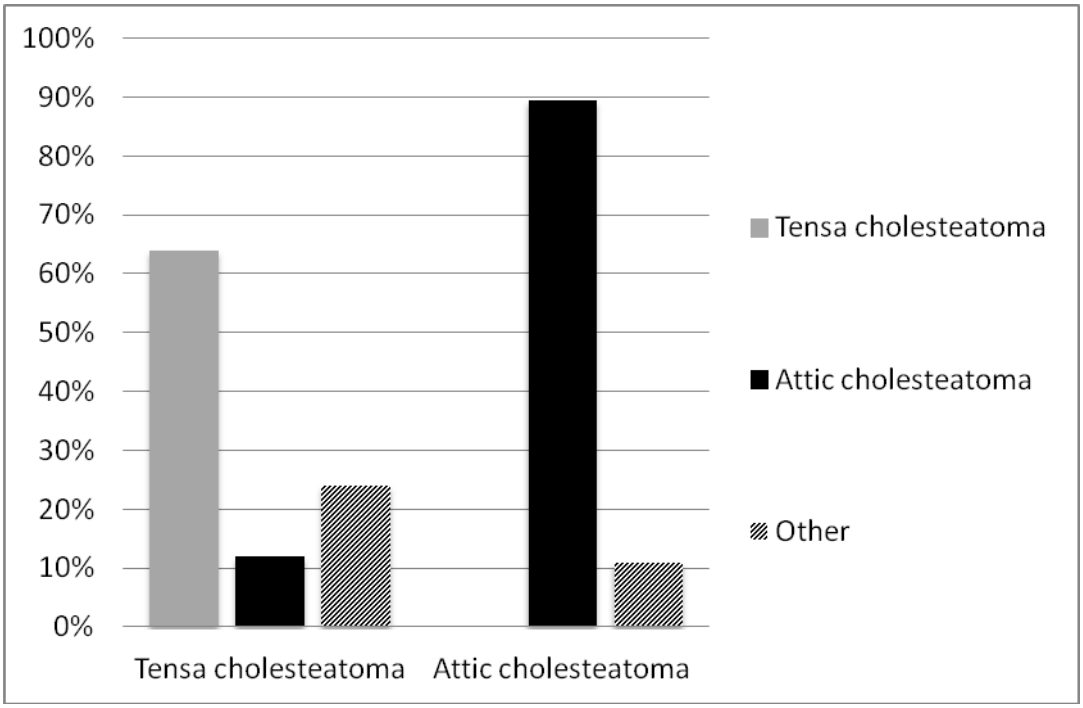

FIG. 3. *Comparison of the cholesteatoma growth patterns in the primary and contralateral ears.*

DISCUSSION

In our study, only about one-third of the contralateral ears were considered normal. Moderate-to-severe tympanic membrane retraction and cholesteatoma were undoubtedly the most prevalent pathological changes. Interestingly, contralateral tympanic membrane retraction occurred mostly at the same location as the cholesteatoma in the primary ear. A similar phenomenon was observed for the cholesteatoma growth patterns in the contralateral ear.

These findings are in agreement with one of the most studied hypotheses for the pathogenesis of chronic otitis media: the continuum theory (10), which suggests that the simplest forms of otitis media may evolve over time to more advanced pathological conditions such as granulation tissue, cholesterol

granuloma and cholesteatoma. After an initial triggering factor, and in the absence of arresting mechanisms, a serous or purulent otitis may become seromucoid, mucoid, and finally chronic. As secretory otitis media is mostly bilateral (11,12), the finding of alterations in both ears, although sometimes in different degrees of severity, such as bilateral cholesteatoma or cholesteatoma in the primary ear and moderate and severe retraction in the contralateral ear, are not surprising. By studying the bilateral middle ears, we observed that if the more damaged ear is already in the final stages of the continuum, then the contralateral ear, also part of this dynamic process, is already close to chronification. Certainly, tympanic membrane retraction is an important, even crucial, step in this continuum. The situation represents what Costa et al used to call the “crystal ball effect” (5), because the more damaged ear frequently predicts the status of the contralateral one.

Our results also reinforce the invagination or retraction theory for attic and tensa cholesteatoma formation. The reasons for tympanic membrane retraction and progress to cholesteatoma are still debated. Eustachian tube dysfunction resulting in impaired middle ear ventilation has been indicated as an important factor. Wolfman and Chole (13) found that cauterization of the eustachian tube in Mongolian gerbils resulted in progressive retraction of the pars flaccida and cholesteatoma in 75% of the animals after 16 weeks. Paradoxically, studies have shown that a patent eustachian tube can also result in middle ear alterations (14,15). Ryding et al. (16) assessed patients having chronic otitis media with effusion and observed changes in the tympanic membrane in 76% of the ears. The ears with a patent tube or tube dysfunction had more pronounced pathology. Bunne and colleagues (17) also found that ears with tympanic membrane

retraction have reduced capacity to equalize pressure and respond to the Valsalva maneuver, when compared with normal controls. According to Bhide (18), retraction of the posterosuperior quadrant of the pars tensa occurs secondary to decreased middle ear pressure and leads to medial displacement of the tympanic membrane. The posterosuperior quadrant appears to be structurally more vulnerable.

Cinamon and Sadé (19,20) believe that distribution of gas in the middle ear involves more than just passive passage from higher to lower pressure. They showed that during swallowing, air is pumped both into and out of the middle ear and patency of the tube is insufficient for its proper ventilation. According to the classical ex-vacuum theory, negative pressure in the middle ear results from functional obstruction of the eustachian tube. The negative intratympanic pressure may be offset by increased transudation and exudation of fluid, resulting in effusion (14). This theory has been questioned by researchers who have shown that transmucosal gas transport is bidirectional and middle ear pressure can be maintained equal to the environment or even be positive without a tubal opening. These findings support the view that gas exchange through mucosa is the primary mechanism for regulating middle ear pressure, while the tube serves as an outlet for excessive positive pressure and can also open to normalize excessive negative pressure. Ar et al. (21) criticize that few have investigated the mechanisms of gas exchange in the inflamed ear, because mucosal inflammation may be the common origin of several cases of chronic otitis media. Kania et al. (22) saw no difference in gas volume changes in the auditory cleft between rats with surgically closed eustachian tubes and controls. Then, any change in gas volume can be attributed to gas exchange through the middle ear mucosa. In middle ear inflammation, both

the mucosal thickness and the passage of air through it increase along with rise in blood flow, which may explain the increased gas loss rate (22,23).

Sudhoff and Tos (2), after observing the retraction of both the pars tensa and the pars flaccida in some children, proposed a four-step concept for the pathogenesis of cholesteatoma that combines the retraction and proliferation theories: (i) the retraction pocket stage; (ii) proliferation of the retraction pocket, subdivided into cone formation and cone fusion; (iii) expansion of cholesteatoma; and (iv) bone resorption. Although bone erosion can occur earlier in the development of tympanic membrane retraction without cholesteatoma formation, the inflammatory process may be involved in both sustenance of negative pressure in the middle ear and progression of tympanic membrane retraction to cholesteatoma.

The tympanic isthmus is the main route of drainage and aeration of the attic chambers and can be occluded by mucosal edema, thick mucus plugs, or retraction of the posterior part of the pars tensa, determining ventilation problems in the epitympanum (24–26). The Prussak space aeration route opens directly into the mesotympanum via the posterior pouch. Histopathological studies have demonstrated that although the dimensions of the posterior pouch vary among individuals, they are bilaterally symmetrical (27). No studies, however, have investigated these aeration routes in patients with cholesteatoma. Congenital variations with obliteration of such routes are possible and can be bilateral and symmetrical, explaining why patients with posterior epitympanic cholesteatoma have a high prevalence of tympanic membrane retraction or cholesteatoma at the same site in the contralateral ear.

We noted that posterior mesotympanic cholesteatoma in the primary ear was associated with 20% of the cases of pars flaccida retraction and 12% of the posterior epitympanic cholesteatomas in the contralateral ear, whereas posterior epitympanic cholesteatoma was related to only 1.8% of the cases of pars tensa retraction and no posterior mesotympanic cholesteatoma in the contralateral ear. These findings suggest that pars flaccida retraction, as well attic cholesteatoma, depends on blockage of the epitympanic aeration routes, which may be congenital and symmetrical. As the pars flaccida is more fragile than the pars tensa, the inflammatory process in the middle ear that leads to pars tensa retraction and cholesteatoma formation can, due to aeration blockage by mucus, granulation tissue, or even retraction of the posterior part of the pars tensa, determine ventilation problems in the epitympanum as well (24–26,28). Regardless of the process involved in tympanic membrane retraction and its progression to cholesteatoma, it seems to be distinguishable according to the growth pattern and similarly occurs in most contralateral ears.

In conclusion, patients with acquired cholesteatoma in one middle ear are very likely to have the same cholesteatoma growth pattern and location of tympanic membrane retraction in the contralateral ear. These findings corroborate the view that chronic otitis media with acquired cholesteatoma is not an isolated event but a constitutional process with a high prevalence of bilaterality.

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