Inner ear disturbances related to middle ear inflammation

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ABSTRACT

The inner and middle ear are connected mainly through round and oval windows, and inflammation in the middle ear cavity can spread into the inner ear, which might induce a disturbance. In cases with intractable otitis media, attention should also be paid to symptoms related to the inner ear. In this paper, middle ear inflammation and related inner ear disturbances are reviewed with a focus on representative middle ear diseases (such as acute otitis media, chronic otitis media, otitis media with anti-neutrophil cytoplastic antibody-associated vasculitis, eosinophilic otitis media, cholesteatoma with labyrinthine fistula, and reflux-related otitis media). Their clinical concerns are then discussed with reference to experimental studies. In these diseases, early diagnosis and adequate treatment are required to manage not only middle ear but also inner ear conditions.

Key Words: middle ear, otitis media, inflammation, inner ear, disturbance

INTRODUCTION

The inner and middle ear are connected mainly through the round and oval windows, and these membranes may allow several toxins to pass from the middle ear into the inner ear. This implies that disturbances of the inner ear could be caused by middle ear inflammation (Figure 1). Symptoms of such disturbances include sensorineural hearing loss (SNHL) and disequilibrium, which occasionally show an intractable clinical course. Irreversible profound SNHL or impairment of equilibrium would severely compromise patient quality of life, even after inflammation in the middle ear has ceased. In this sense, control of middle ear inflammation in the early stage is essential to decreasing the risk of inner ear disturbances.

In this paper, representative middle ear diseases with inflammation and related inner ear disturbances are reviewed and their clinical concerns are discussed with reference to the results of experimental studies.

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REPRESENTATIVE MIDDLE EAR DISEASES

**Acute otitis media (AOM)**

Inner ear disturbances related to AOM have been demonstrated in experimental studies.\(^1\) The cochlear lateral wall is a target of cochlear damage following endotoxin-induced otitis media.\(^2\) In a study using a model of endotoxin-induced otitis media, cochlear blood flow was significantly decreased and vacuolar changes were seen in the stria vascularis at 24 h after inoculation of endotoxin into the middle ear cavity (Figure 2).\(^7\) After 14 days, cochlear blood flow returned to normal and the cochlear lateral wall displayed a histologically normal appearance. Clinically, elevated thresholds at high frequencies on audiometry return to normal ranges in most cases, indicating reversal of inner ear damage.

The fluid-attenuated inversion recovery (FLAIR) sequence of magnetic resonance imaging (MRI) has recently been applied to the inner ear,\(^8\) enabling the demonstration of hemorrhage and high protein concentrations in lesions.\(^11\) The blood-labyrinth barrier (BLB) exists in the lateral wall, and maintains the composition of the inner ear fluid; the function of the BLB is to protect the inner ear from toxic substances by selectively limiting the entry of substances into the inner ear. Prolonged signal hyperintensity in the inner ear was detected on FLAIR MRI in a patient with AOM, which would suggest long-lasting breakdown of the BLB in cases with aggressive middle ear inflammation.\(^12\) Animal studies have focused on prevention of inner ear disturbance following AOM, such as through the use of glucocorticoids,\(^13\) or nitric oxide synthase (NOS).\(^15\) The effectiveness of intratympanic dexamethasone or NOS inhibitors has been demonstrated in the treatment of cochlear lateral wall damage caused by AOM.\(^17\) Steroid injection is commonly applied clinically for reducing inner ear disturbances due to AOM, as proposed from animal studies.\(^18\)

**Chronic otitis media (COM)**

Chronic inflammation in the middle ear represents a high risk factor for inner ear disturbances. Evaluation of risk factors on computed tomography (CT) findings for COM-related SNHL in
patients with unilateral COM has shown that the presence of soft-tissue density in the antrum increased the odds ratio of SNHL to 3.8.\textsuperscript{19} Age, disease duration, and the presence of soft tissue density in the round window niche were also independent predictors of SNHL. Yoshida \textit{et al.} investigated relationships between temporal bone CT findings and SNHL in ears with COM.\textsuperscript{20} Impairment of bone conduction seems to worsen as the course of the disease progresses, especially at higher frequencies with a smaller mastoid area.\textsuperscript{20} Another study reported age, osseous disruption, perforation size, and type of retraction as predictors for SNHL in COM.\textsuperscript{21} In a study of cochlear pathology in human temporal bones with otitis media, pathological findings were serofibrinous precipitates and inflammatory cells in the scala tympani of the basal turn and cochlear aqueduct, significant loss of outer and inner hair cells, and significantly decreased area of the stria vascularis in the basal turn of the cochlea.\textsuperscript{22} Considering such reports, surgical management in the early stage should be planned in cases meeting the indications to decrease the risk of inner ear disturbance.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Electron microscopic findings for the stria vascularis in rats at 24 h after inoculation of endotoxin into the middle ear cavity. Intercellular spaces between intermediate cells are markedly enlarged (asterisks), and marginal cells project towards the endolymphatic space (arrows).
}
\end{figure}

\textit{Otitis media with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (OMA AV)}

Antineutrophil cytoplasmic antibody (ANCA) is the antibody against neutrophil and monocyte lysosomal enzymes, and granulomatosis with polyangiitis is a disease of ANCA-associated vasculitis (AAV). Systemic AAV can present various otological symptoms during the clinical course, whereas the less common localized AAV presents only with otological symptoms such as otitis media and hearing loss.\textsuperscript{23} OMAAV shows novel clinical features, and may be categorized as a
Michihiko Sone

subentity of AAV (24). FLAIR MRI shows signal hyperintensity in the inner ear among cases with OMAAV and imaging assessment has been introduced as a useful method for evaluating inner ear disturbances associated with this disease. Increased signals from the cochlea on post-contrast imaging are stronger on the side with the worse hearing level (Figure 3). In the case shown in the figure, hearing levels were 91.7 dB in the right and 60.0 dB in the left. High signals on MRI indicate breakdown of the BLB, and hearing levels improved in parallel with decreases in signal intensity after treatment was initiated. One mechanism proposed for reversible SNHL involves homeostatic function, such as the stria vascularis or spiral ligament, and the case in the figure supports that mechanism for reversible SNHL proposed by Yoshida et al. Irreversible breakdown of the BLB could lead to damage to the hair cells, which would lead to permanent SNHL.

For control of the disease, initial immunosuppressive therapy that includes corticosteroid, cyclophosphamide or methotrexate is strongly recommended for achieving long-term remission of OMAAV.

Eosinophilic otitis media (EOM)

EOM is characterized by a highly viscous effusion with eosinophils and high levels of immunoglobulin (Ig)E in the middle ear effusion. This intractable otitis media could cause severe SNHL. In cases with EOM, eosinophilic inflammation-related substances and IgE were found to be closely related to the exacerbation of SNHL at high frequencies. Diagnostic criteria for EOM resistance to conventional treatment are otitis media with effusion or COM with viscous eosinophil-dominant effusion with or without granulation tissue formation, an association with bronchial asthma, nasal polyposis, and chronic rhinosinusitis. A significant association has been found between the severity of EOM and obesity, as well as with the duration of bronchial asthma. Uchimizu et al. reported interleukin (IL)-5, IL-2, macrophage inflammatory protein –1α, and IL-1ra as the important factors involved in the pathogenesis of EOM, and neutrophils are also involved in the middle ear inflammation in EOM. In an experimental study of inner ear injury using an animal model of EOM, severe morphological damage of the organ of Corti and infiltration of numerous eosinophils, red blood cells, and plasma cells into the perilymph were reported.
Inner ear disturbances

In clinical practice, topical application of steroid to the middle ear cavity after suction withdrawal of viscous effusion, and oral administration of anti-allergic drugs are common. With systemic or topical steroid administration, long-term anti-IgE therapy was reported to improve clinical ear symptoms of EOM and SNHL.\textsuperscript{30}

*Cholesteatoma with labyrinthine fistula*

Risk factors for SNHL in cases with COM are considered to be longer duration of disease, older age and the presence of cholesteatoma.\textsuperscript{31} Cholesteatomas invading the inner ear structures, which result in labyrinthine fistula, can cause severe inner ear disturbances. Inadequate surgical manipulation might lead to profound SNHL and prolonged vestibular symptoms. Several points have been noted concerning risk factors for inner ear disturbances, including existence of nystagmus or infection, and large bone defects on CT. A small fistula, however, could also cause severe inner ear disturbances, and preoperative prediction of such complications is not easy. One of the main disturbances in the inner ear due to cholesteatoma with labyrinthine fistula is breakdown of the BLB. Signal intensities on FLAIR MRI have been reported to correlate more strongly than CT findings with the clinical status of patients with labyrinthine fistulae caused by cholesteatoma, and to accurately reflect the extent of inner ear dysfunction associated with the disease.\textsuperscript{32} Kobayashi et al.\textsuperscript{33} reported that preservation of cochlear function despite involvement of the lateral semicircular canal indicates relative independence of the labyrinthine fluid system of the cochlea from that of the vestibular labyrinth. However, a finding of signal hyperintensities on FLAIR MRI suggests breakdown of the normal labyrinthine fluid system.

*Reflux-related otitis media*

Supraesophageal reflux of gastric contents induces various manifestations in the otorhinolaryngological region, including otitis media. High pepsin/pepsinogen (PG) concentrations in middle ear effusion (MEE) have been reported in both children and adults.\textsuperscript{34,35} A study involving direct injection of rabbit gastric contents into the middle ear cavities of the animals showed inflammation and expression of cytokines in the mucosa.\textsuperscript{36} With gastric contents, reflux of bilirubin and biliary acid into the middle ear cavity in adults has been demonstrated,\textsuperscript{37,38} inducing more severe inflammation in the middle ear.\textsuperscript{39}

Inner ear disturbances of reflux-related otitis media remain unclear, but elevated bone conductance thresholds at low frequencies have been reported in patients with high PG concentrations in MEE.\textsuperscript{40} In a study of cochlear function in rats with experimental gastric reflux, decreased responses of otoacoustic emissions were reported, suggesting that acidified gastric pepsin causes hearing loss due to inner ear ototoxicity.\textsuperscript{41} Along with anti-reflux treatment using proton pump inhibitors, instruction about lifestyle-related factors leading to reflux is important to improve reflux-related otitis media.\textsuperscript{38}

**CONCLUSION**

In cases with intractable otitis media, attention should always be paid to symptoms related to the inner ear. Early preventive treatment is preferable to avoid severe SNHL or disequilibrium.

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