Detection of postoperative cholesteatoma with diffusion-weighted MR imaging

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Abstract: Objectives: To highlight the reliability of DW MRI in the identification of the postoperative cholesteatoma in confrontation with the surgical finding. Data Sources: Medline databases (PubMed, Medscape, ScienceDirect. EMF-Portal) and all materials available in the Internet from 2006 to 2016. Study Selection: The initial search presented 170 articles of which 44 met the inclusion criteria. Data Extraction: If the studies did not fulfill the inclusion criteria, they were excluded. Study quality assessment included whether ethical approval was gained, eligibility criteria specified, appropriate controls, adequate information and defined assessment measures. Data Synthesis: Comparisons were made by structured review with the results tabulated. Findings: Cholesteatoma is a common problem encountered in otology clinics. The major argument in favour of closed technique is the presence of a normal ear canal, which avoids the need for regular aural toilet and also enables the better use of a hearing aid. In a preoperative patient, high-resolution CT (computerized tomography) and conventional T1- and T2weighted magnetic resonance imaging (MRI) scan complement each other in providing detailed assessment of the extent of the disease and the anatomy of the temporal bone. Following mastoid surgery, both of these imaging modalities cannot reliably distinguish between residual or recurrent disease and other post-operative changes such as fuid, granulation or infammatory tissue. Recent advances in MRI techniques such as "diffusion weighted" and "delayed post-gadolinium" sequences have suggested that these imaging modalities may help in the diagnosis of residual cholesteatoma. In diffusion- weighted MRI scans, several different types of imaging sequences have been described for the evaluation of cholesteatoma. DW-weighted MRI is based on the principle of random microscopic motion (Brownian motion) of water molecules. A pair of pulsed magnetic fields are applied within a given time interval and the net shift of water molecules is observed between the two pulses. This "diffusion" of water molecules differs in each biological tissue. Conclusion: DW EPI fails to demonstrate middle ear cholesteatoma with a size smaller than 5 mm due to susceptibility artifacts, lower imaging matrix and relatively thick slices. Recent papers have highlighted the advantages of non-echoplanar-based diffusion-weighted sequences compared to DW EPI. [Ashraf S. El-hamshary; Abo Bakr E.; Mohamed I. Hassan and Manar M.S. Selim. Detection of postoperative cholesteatoma with diffusion-weighted MR imaging. N Y Sci J 2016;9(2):71-78]. ISSN 1554-0200 (print); ISSN 2375-723X (online). http://www.sciencepub.net/newyork. 12. doi:10.7537/marsnys09021612.

Key words: postoperative cholesteatoma, diffusion-weighted, magnetic resonance imaging.

1. Introduction

Cholesteatoma of the middle ear are divided into attic cholesteatoma, sinus cholesteatoma and tensa-retraction cholesteatoma. This classification is proposed for better understanding of the pathogenesis of cholesteatoma and is also important for evaluation of the natural history, prognosis, surgical methods and results⁽¹⁾.

 $Tos^{(2)}$ proposed a four-step concept for pathogenesis of cholesteatoma combining the retraction and the proliferation theory: the retraction pocket stage, the proliferation stage of the retraction pocket, expansion stage of cholesteatoma and bone resorption stage.

Canal wall-up tympanoplasty (CWUT) is a major surgical procedure for the treatment of acquired cholesteatoma of the middle ear; however, a surgical second look is often required 9–18 months after the primary surgical procedure to rule out a residual cholesteatoma due to a possibly incomplete removal of the lesion⁽³⁾. In the past decade, **Tierney** *et al.*⁽⁴⁾ have evaluated the contribution of imaging in the detection of postoperative cholesteatomas, in order to avoid a surgical revision.

Imaging needs to be able to differentiate residual or recurrent disease from granulation tissue, inflammatory tissue or fluid within the middle ear cavity and mastoid cavity. High-resolution computed tomography (HRCT), conventional magnetic resonance imaging (MRI), and delayed contrast MRI have all been used in detecting postoperative cholesteatoma. Although delayed contrast MRI performs better than HRCT and conventional MRI, the sensitivities and specificities of these different imaging methods are relatively poor⁽⁵⁾.

Fitzek *et al.*⁽⁶⁾ described several different types of imaging sequences in diffusion- weighted MRI scans including single-shot echo-planar imaging (EPI) and more recently "non" echoplanar (non-EPI) sequences have also been described for the evaluation of postoperative cholesteatoma.

De Foer *et al.* ⁽⁷⁾ have highlighted the advantages of non-echoplanar-based diffusion-weighted sequences.

These sequences are most frequently single shot or multishot-based turbo spin echo diffusion-weighted sequences. They have a thinner slice thickness, a slightly higher resolution, and a complete lack of artefacts compared to echo planar diffusion-weighted sequences.

2. Materials and Methods Search Strategy:

We reviewed papers from Medline databases which are (Pub Med, Medscape, and ScienceDirect) and also materials available in the Internet. We used postoperative cholesteatoma, diffusion-weighted, magnetic resonance imaging as searching terms. In addition, we examined references from the specialist databases EMF-Portal (http://www.emf-portal.de), reference lists in relevant publications and published reports. The search was performed in the electronic databases from 2006 to 2016.

Study Selection:

All the studies were independently assessed for inclusion. They were included if they fulfilled the following criteria:

Inclusion criteria of the published studies:

-Published in English language.

-Published in peer-reviewed journals.

-If a study had several publications on certain aspects we used the latest publication giving the most relevant data.

Data Extraction:

If the studies did not fulfill the above criteria, they were excluded such as, Studies on diffusionweighted MR imaging in postoperative cholesteatoma, reports without peer-review, not within national research programme, letters/comments/editorials/news and studies not focused on diffusion-weighted MR imaging in postoperative cholesteatoma.

Quality Assessment:

The quality of all the studies was assessed. Important factors included, study design, attainment of ethical approval, evidence of a power calculation, specified eligibility criteria, appropriate controls, adequate information and specified assessment measures. It was expected that confounding factors would be reported and controlled for and appropriate data analysis made in addition to an explanation of missing data.

Data Synthesis:

A structured systematic review was performed with the results tabulated.

3. Results

The middle ear can be divided into three compartments: the mesotympanum, hypotympanum, and epitympanum. Main elements of the middle ear are: the fibro cartilaginous eustachian tube, the tympanic cavity and its mucosa and the mastoid air cell system⁽⁸⁾.

Although Eustachian tube dysfunction in the final common pathway for several types of pathologic changes, in the actual tubal lumen resulting in negative middle ear pressure and subsequent retraction pocket formation, an attic retraction pocket could occur thorugh normal tubaric function; therefore, there should be other factors in the pathogenesis of attic cholesteatoma⁽⁹⁾.

For the first time, **Chatellier and Lemoine**⁽¹⁰⁾ introduced the concept of the "epitympanic diaphragm" which was described as the floor of the epitympanum and consisted of the incus, malleus and their folds. They thought that attic and mastoid aeration would occur through atympanic isthmus located between the anterior crus of the stapes and the tensor tympani tendon.

Later on, **Proctor** ⁽¹¹⁾ described a posterior isthmus, medially to what he called the medial incudal fold, as a small opening between the middle ear and the epitympanic space, with the purpose of aerating the middle ear cleft.

Aimi⁽¹²⁾ described the tympanic isthmus as a narrow passage between the tubotympanic cavity and the atticomastoid space. He observed that obstruction of this tympanic isthmus is common in various types of middle ear disease.

Palva and Johnsson⁽¹³⁾ described the "epitympanic diaphragm" which consists of three malleal ligament folds (the anterior, lateral and posterior), the posterior incudal ligamental fold, and the two purely membranous folds (the tensor fold and the lateral incudomalleal fold), together with the malleus and incus.

Palva and Ramsay⁽¹⁴⁾ noted that all epitympanic compartments receive their aeration via the large tympanic isthmus, between medial part of the posterior incudal ligament and the tensor tendon. Also, **Palva** *et al.*⁽⁹⁾ observed that the aeration pathway from the Eustachian tube leads directly to the mesotympanic and hypotympanic spaces, where as the epitympanum is away from the direct airstream and is only aerated through the tympanic isthmus.

Acquired cholesteatoma of the middle ear are divided into:

(1) Attic cholesteatoma, originating from the Sharpnell's membrane and extending primary into the attic.

(2) Sinus cholesteatoma, originating from the postero-superior retraction of the pars tensa and extending primary into the tympanic sinuses. From here, it may extend along the prominence of the facial nerve, medial to the incus body, into the posterior attic and antrum, while the anterior part of the tympanic cavity and the anterior attic are not involved.

(3) Tensa-retraction cholesteatoma, originating from an entirely retracted pars tensa, draping over the posterior and anterior walls of the tympanic cavity, extending from here into the hypotympanic cells and tubal orifice. Furthermore, it may extend, medially to the malleus folds, towards the posterior and anterior attic.

This classification is proposed for better understanding of the pathogenesis of cholesteatoma and is also important for evaluation of the natural history, prognosis, surgical methods and results⁽¹⁾.

Several theories on pathogenesis of cholesteatoma have been discussed:

(1) **Retraction theory:** Based on a retraction of the pars tensa or the Sharpnell's membrane as a result of chornic dysfunction of the Eustachian tube⁽¹⁵⁾.

(2) Papillary proliferation theory: Based on infection leading to proliferation of the epithelial cones in the basal layers of the keratinizing epithelium of the pars tensa or the Sharpnell's membrane⁽¹⁶⁾.

(3) Immigration theory: Based on ingrowth of the squamous epithelium through preexisting peripheral perforation⁽¹⁷⁾.

(4) Metaplasia theory: Based on the metaplasia of the inflamed middle ear epithelium into keratinizing squamous epithelium⁽¹⁸⁾.

Clinically, it is difficult to find any support for the immigration theory; **Tos**⁽¹⁹⁾ have never observed an acute perforation of the pars tensa or the Sharpnell's membrane allowing immigration of the keratinizing epithelium through it. They have not observed any cholesteatoma starting somewhere in the antrum due to metaplasia and expanding outwards through the pars tensa or the Sharpnell's membrane.

Indeed, there is some evidence for retraction and proliferation theories for a certain stage of cholesteatoma formation. There is a clinical evidence for formation of retraction, but there is no exact explanation for the transition from a retraction pocket to an active and expanding cholesteatoma. There is a combination of the retraction theory and the proliferation theory could explain the pathogenesis of the acquired middle ear cholesteatoma⁽¹⁹⁾.

As a possible explanation based on clinical and immunohistochemical findings, **Tos**⁽²⁾ **and Tos**⁽¹⁹⁾ have demonstrated proliferating keratinocytes within the epithelial cones, growing towards the underlying perimatrix.

They proposed a four-step concept for pathogenesis of cholesteatoma combining the retraction and the proliferation theory:

(1) The retraction pocket stage.

(2) The proliferation stage of the retraction pocket, subdivided into:

(a) Cone formation.

(b) Cone fusion.

(3) Expansion stage of cholesteatoma.

(4) Bone resorption stage⁽¹⁹⁾.

Basic principle of DWI:

At human body temperature, random water molecules migrate approximately 30 um over 50 ms. but only if there are no barriers to their motion. Water movement in tissues is neither entirely free nor random, being modified by interactions with hydrophobic lipid-containing cell membranes, intracellular organelles, macromolecules and by-flows within tubular channels such as blood vessels and ducts. Thus tissue water motion is related to its microscopic structure. The thermally driven motion of water is uniquely assessed by DWI. MRI is able to measure the water diffusivity by the application of diffusion sensitizing gradients (motion probing gradients) to T2-weighted spin-echo sequences usually with echoplanar readouts of the data. Signal loss on DWI is proportional to both the free motion of water molecules and the diffusion gradient strength used⁽²⁰⁾.

The strength and duration of application of diffusion sensitizing gradients is indicated by their "bvalue". Generally, a range of b-values (two or more) are used in a DW-MRI study to detect the water diffusion properties of tissues. In the absence of diffusion sensitizing gradients (b-value=0 s/mm2), free water appears bright because of intrinsic T2weighting. In images acquired with low b values (50-100 s/mm2), vessels and cerebrospinal fluid show marked signal attenuation because water molecules will have moved over a relatively large distance during the time of application of the diffusion sensitizing gradients. Because signal intensity from blood vessels is attenuated on low b-value images, these images are often termed "black blood" images⁽²¹⁾.

With increasing b-values, signal intensity attenuates steadily in other tissues, initially attenuating in free water (e.g. urine in the bladder), then in glandular tissues (e.g. prostate, salivary glands and pancreas) and then in tissues showing highly organized cellular structure such as the liver. Because water movement is relatively impeded in highly packed tissues such as tumors, very cellular tissues appear persistently bright against a darkening background at high b-values of 500–1,000 s/ mm2. For the same reasons, several normal but highly cellular tissues also appear bright on high b-value images, including the brain, spinal cord, spleen (variable) and normal lymphatic tissues (tonsils, adenoids, lymph nodes) (table 1)⁽²¹⁾.

Cholesteatoma is often treated surgically using canal wall-preserving techniques. Clinical and otoscopic diagnosis of residual or recurrent disease after this form of surgery is unreliable and thus radiological imaging is often used prior to mandatory "second-look" surgery⁽⁵⁾.

Unlike recurrent cholesteatoma, developing from recurring retraction pockets or defects in the tympanic membrane reconstruction, residual cholesteatoma cannot be detected by a simple clinical examination⁽²²⁾.

Several methods, such as Eustachian tube endoscopy, have been proposed to detect residual cholesteatomas. However, these techniques are not routinely performed and canal wall-up (CWU) tympanoplasties for middle ear cholesteatoma usually require second-look surgery to rule out the presence of residual cholesteatoma. Identification of residual cholesteatoma and differentiation from postoperative granulation tissue by non invasive technique to avoid second look surgery are of great value⁽⁴⁾.

Imaging needs to be able to differentiate residual or recurrent disease from granulation tissue, inflammatory tissue or fluid within the middle ear cavity and mastoid cavity. High-resolution computed tomography (HRCT), conventional magnetic resonance imaging (MRI), and delayed contrast MRI have all been used in detecting postoperative cholesteatoma. Although delayed contrast MRI performs better than HRCT and conventional MRI, the sensitivities and specificities of these different imaging methods are relatively $poor^{(5)}$.

Cholesteatomatous tissue shows an intermediate to hypointense signal on T1W images and appears hyperintense on the corresponding T2W images. This hyperintensity is, however, significantly less as compared to that seen in inflammatory lesions⁽⁷⁾.

The use of delayed postcontrast T1W sequences demonstrating postoperative residual in Performing cholesteatoma. а T1W sequence after intravenous gadolinium 45 minutes (a paramagnetic MRI contrast agent), allows a distinction to be made between avascular, non enhancing cholesteatoma and delayed homogenous enhancement seen in inflammatory and/or scar tissue. Delayed postcontrast imaging is a time consuming examination and comes with an additional cost to the patient. In very young children general anaesthesia is required to obtain optimal diagnostic images which also adds to the cost of the study. In addition, the rationale behind this technique was that the postoperative scar tissue takes time to enhance and that early scanning will result in false-positive results⁽²³⁾. These specific MRI findings differentiating cholesteatoma and inflammatory/granulomatous lesions are summarized in Table $(2)^{(7)}$.

Interpretation	ADC Maps	Signal Intensity On high- b -value DW images
Generally, high-cellularity tumor; rarely abscess, viscous fluids, or blood products	Û	Î
T2 shine through; liquefactive necrosis	Î	Û
Fluid; necrosis; lower cellularity; occasionally well-differentiated Adenocarcinomas		
Fibromuscular tissues, fat, susceptibility artifact	Ţ	
Mature fibrous tissue with low water content		

Table (1): Image Interpretation Guidelines for DW MR Imaging⁽²¹⁾.

Low signal

High signal <===

Intemediate signal

MRI sequence	Cholesteatoma	Inflammatory tissue
T1W coronal	Iso-heterointense	Iso-hypointense
T2W coronal	Iso-hyperintense	Hyperintense
TSE diffusion coronal	Diffusion restriction	No diffusion restriction
Delayed postcontrast T1W coronal	No enhancement/mild rim enhancement	Homogenous enhancement

Table (2): MRI findings on four sequences differentiating cholesteatoma from inflammatory/granulomatous lesions⁽⁷⁾

4. Discussion

Acquired cholesteatoma consists of epithelial debris that results from desquamation of the lining of the external auditory canal and outer lining of the tympanic membrane. The treatment is surgical resection. However, complete surgical extirpation may be difficult in advanced lesions. After surgery, it is distinguish difficult to between recurrent cholesteatoma and granulation tissue from both clinical and radiologic standpoints. The middle ear cavity is difficult to visualize because of postoperative scarring and thickening of the tympanic membrane. The imaging appearance on both MR images and CT scans is often nonspecific⁽²⁴⁾.

Patients with well-aerated postoperative mastoid bowls and middle ear cavities can be easily evaluated with CT. However, if a soft-tissue mass in the cavity of the middle ear is seen on high-resolution CT, diagnosis of the mass is not possible because cholesteatoma, mucoid secretion, granulation tissue, fibrous tissue, and cholesterol granuloma cannot be differentiated from one another on high-resolution CT. As a result, many surgeons have to perform a followup procedure to determine the cause of the mucosal thickening⁽²⁵⁾.

Diffusion weighted MRI (DWI) is a newly developed differentiating tool between residual cholesteatoma and granulation tissue. The differentiating point is that only cholesteatoma shows high signal intensity on diffusion-weighted MR images. Other tissues that can be found in the middle ear cavity after surgery such as granulation tissue, fibrous tissue, cholesterol granuloma, or serous fluid show low signal intensity on diffusion- weighted MR images⁽²⁶⁾.

Diffusion-weighted imaging (echo-planar imaging (EPI), non-echo planar DWI) is a technique that measures the molecular diffusion of water (Brownian motion) within the tissues⁽²⁷⁾. However, numerous artefacts can be generated during acquisition of EP DW MR imaging such as chemical shift and motion artefacts. With the use of higher magnetic fields, these artefacts and image distortions on EP DW imaging are even more pronounced. Also in the temporal bone region, the interface between air, bone and the temporal lobe is in particular prone to susceptibility artifacts⁽⁷⁾.

Khemani *et al.*⁽⁵⁾ have favoured non-echo-planar DWI (single shot or multishot-based turbo spin echo DWI) as it is less susceptible to the skull base distortion that can occur because of the presence of an air–bone interface. Another solution for this problem has been described that combines echo-planar imaging with an image motion suppression technique known as PROPELLER DWI.

Multishot fast spin-echo DWI-PROPELLER technique is considered the most recent method for the diagnosis of residual cholesteatoma. The ability of DWI to be used consistently to evaluate the temporal bone is hindered by image distortion caused by susceptibility artifacts, chemical-shift artifacts, and ghosts in the phase-encoding direction. This is due to the high bone attenuation of the inner ear and the numerous air-bone interfaces present within the mastoid air cells and the middle ear cavity. With PROPELLER MR imaging, the marked reduction in off-resonance artifacts is primarily caused by the type of sequence (fast SE): Fast SE imaging is less sensitive to changes in the constant magnetic induction field, because of multiple 180 refocusing pulses. Reduction of susceptibility artifacts is particularly important for adequate visualization of the middle ear⁽²⁸⁾

The main idea of PROPELLER DWI is radial kspace filling technique, so MR imaging datasets are acquired in multiple overlapping radial sections, each of which includes data sampled from the center to the periphery of k-space⁽²⁹⁾.

Yet its main disadvantage is low spatial resolution, which results from the fact that the

periphery of k-space is more sparsely filled than its central region. It is difficult with radial sampling techniques to achieve the high spatial resolution commonly expected in clinical practice because of the increased acquisition time. Also it can be performed only with axial sections, which does not optimize visualization of the tegmen region⁽³⁰⁾.

Cholesteatoma is composed of an enlarging collection of exfoliated keratin within a sac of stratified squamous epithelium that shows no change in signal intensity on contrast-enhanced MR images. Conversely, granulation tissue shows enhancement only on delayed contrast-enhanced images owing to its fibrous nature and, possibly, to the microvascular thrombosis phenomenon. It is necessary to obtain delayed contrast-enhanced images with a delay of 30–45 min after contrast material administration ⁽³¹⁾.

Ayache et al. ⁽²³⁾ achieved high diagnostic results with DW-MRI as they have correctly detected 17 out of 19 residual cholesteatoma with overall sensitivity of 90%; specificity of 100%; positive predictive value of 100%; negative predictive value of 92%. They missed two lesions which were <3 mm.

De Foer *et al.* ⁽³²⁾ showed that the concurrent use of nonecho planar hyperintensive signal in DWI and delayed contrast-enhanced MR yielded no significant increase in diagnostic performance over the use of non-echo planar DWI alone.

Maheshwari and Mukherji⁽²⁴⁾ described the diffusion-weighted imaging findings and apparent diffusion coefficient values in a case of recurrent cholesteatoma. This case suggested possible differentiation of cholesteatoma from granulation tissue on the basis of diffusion-weighted imaging findings.

Jindal *et al.* ⁽³³⁾ determined whether the diffusionweighted (DW) magnetic resonance imaging scan can reliably detect residual or recurrent cholesteatoma after mastoid surgery. They suggested that non-EPI such as half-Fourier acquisition single-shot turbo spin echo sequences are more reliable in identifying residual or recurrent cholesteatoma

Fahmy and Ragab⁽³⁴⁾ determined the role of PROPELLER diffusion-weighted MR imaging combined with conventional MR imaging for the detection of residual cholesteatoma in patients who have undergone middle ear surgery. They concluded that DWI with ADC map is useful in the detection of secondary cholesteatoma and would decrease the need for un-necessary second canal up operation.

Lingam *et al.* ⁽³⁵⁾ determined whether there is a difference between the ADCs of postoperative middle ear cleft cholesteatoma and those of noncholesteatomatous tissue on half-Fourier acquisition single-shot turbo-spin echo DW images and to determine, with interobserver agreement, a

predictive accuracy for diagnosis of postoperative middle ear cleft cholesteatoma. They showed that the ADC value of cholesteatoma on half-Fourier acquisition single-shot turbo-spin echo DW images was significantly lower than that of noncholesteatomatous tissue and was accurate for detection of postoperative cholesteatoma.

Conclusion:

(1) Cholesteatoma is a common problem encountered in otology clinics.

(2) The major argument in favour of closed technique is the presence of a normal ear canal, which avoids the need for regular aural toilet and also enables the better use of a hearing aid.

(3) In a preoperative patient, high-resolution CT (computerized tomography) and conventional T1- and T2-weighted magnetic resonance imaging (MRI) scan complement each other in providing detailed assessment of the extent of the disease and the anatomy of the temporal bone.

(4) Following mastoid surgery, both of these imaging modalities cannot reliably distinguish between residual or recurrent disease and other postoperative changes such as fuid, granulation or infammatory tissue.

(5) Recent advances in MRI techniques such as "diffusion weighted" and "delayed post-gadolinium" sequences have suggested that these imaging modalities may help in the diagnosis of residual cholesteatoma.

(6) In diffusion- weighted MRI scans, several different types of imaging sequences have been described for the evaluation of cholesteatoma.

(7) DW-weighted MRI is based on the principle of random microscopic motion (Brownian motion) of water molecules.

(8) A pair of pulsed magnetic fields are applied within a given time interval and the net shift of water molecules is observed between the two pulses.

(9) This "diffusion" of water molecules differs in each biological tissue.

(10) DW EPI fails to demonstrate middle ear cholesteatoma with a size smaller than 5 mm due to susceptibility artifacts, lower imaging matrix and relatively thick slices.

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No Conflict of Interests.

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