Utility of Magnetic Resonance Imaging in Differentiating Cerebrospinal Fluid Leak from Middle Ear Effusion

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Abstract

Objective. To demonstrate the clinical utility, sensitivity, and specificity of standard magnetic resonance imaging (MRI) sequences in differentiating temporal bone cerebrospinal fluid leaks from all other middle ear effusions.

Study Design. Retrospective imaging review.

Setting. Academic medical center.

Subjects. Patients with cerebrospinal fluid leaks or other middle ear effusions who also underwent MRI.

Methods. Patients were assigned to cerebrospinal fluid leak and other effusion cohorts based on clinical course, findings at surgery/myringotomy, and beta-2 transferrin fluid analysis. Reviewers blinded to the clinical outcome examined T1-weighted, T2-weighted, diffusion-weighted, fluid-attenuated inversion recovery (FLAIR), and 3-dimensional (3D) acquired T2-weighted MRI sequences. For each sequence, fluid imaged in the temporal bone was graded as either similar or dissimilar in signal intensity to cerebrospinal fluid in the adjacent subarachnoid space. Signal similarity was interpreted as being diagnostic of a leak. Test characteristics in predicting the presence of a leak were calculated for each series.

Results. Eighty patients met criteria (41 leaks, 39 other effusions). The 3D T2 series was 76% sensitive and 100% specific in diagnosing a leak, and FLAIR was 44% sensitive and 100% specific. The T1-weighted (73% sensitive, 69% specific), T2-weighted (98% sensitive, 5.1% specific), and diffusion-weighted (63% sensitive, 66% specific) series were less useful.

Conclusions. MRI, with attention to 3D T2 and FLAIR series, is a noninvasive and highly specific test for diagnosing cerebrospinal fluid leak in the setting of an indeterminate middle ear effusion.

Keywords

magnetic resonance imaging, cerebrospinal fluid leak, skull base, temporal bone, imaging.

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Middle ear effusions (MEEs) are frequently encountered by otolaryngologists. The problem is typically transient in adults, as the eustachian tube reopens, air enters the temporal bone, and the fluid subsequently resorbs or drains into the nasopharynx. In cases of persistent MEE, bothersome conductive hearing loss may prompt more active management. Myringotomy and drainage of the MEE often lead to rapid symptomatic improvement. However, if high-volume otorrhea persists, a revised diagnosis of temporal bone cerebrospinal fluid (CSF) leak may be considered.

When fluid is available for sampling, beta-2 transferrin assay is a rapid, widely available, highly sensitive, and highly specific gold standard test to diagnose a CSF leak. The test can detect small amounts of the beta-2 transferrin protein, which is present only in CSF and vitreous humor, even when the sample is diluted by other body fluids. Sensitivity of this assay in clinical practice may be hampered by sampling error, as it can be difficult to obtain an adequate volume of fluid in some cases.
Chronic MEE due to eustachian tube obstruction typically takes on a characteristic amber hue, but in the event of more transparent MEE or other clinical factors suggesting a CSF leak, this alternate diagnosis may also be suspected. In such cases, a noninvasive means to detect CSF in the middle ear or temporal bone would be desirable.

Magnetic resonance imaging (MRI) utilizes specific pulse sequences of radiofrequency energy to interrogate the molecular properties of fluid and soft tissue. Responses of energized molecules in the magnetic field lead to varying signal intensities on the generated images. Different fluids may take on characteristic appearances with certain sequences, such as fluid-attenuated inversion recovery (FLAIR), with which high protein content generates a brighter-appearing fluid.

With the aforementioned clinical situations in mind, we sought to investigate the utility of standard MRI sequences in differentiating CSF in the temporal bone from all other MEEs.

**Materials and Methods**

Prior to chart review, institutional review board approval was obtained (University of Cincinnati 2017-2418). The electronic medical record of an academic medical center was queried for patients with a diagnosis code entry for MEE or chronic otitis media with effusion (381.X, H65.X; International Classification of Diseases, Ninth Revision or Tenth Revision). Clinical notes and beta-2 transferrin test results were reviewed. Patients were included in the non-CSF MEE group if there was documentation of an effusion with resolution on subsequent visits, either spontaneously or with myringotomy and drainage. Patients with CSF leaks were selected from a surgeon-maintained database of patients with spontaneous leaks. Patient lists were cross-referenced against the institutional radiology database to include only patients who also underwent MRI scans within 1 year of the diagnosis code entry.

Radiology reports were reviewed for mention of fluid in the ipsilateral temporal bone at the time of the scan. Exclusion criteria included inadequate or unavailable imaging, absent or poorly visualized middle ear or mastoid effusion identified at time of the scan, and inadequate clinical follow-up to confirm the diagnosis.

For all scans, available axial T1-weighted, T2-weighted, FLAIR, diffusion-weighted, and 3-dimensional (3D) T2 (eg, FIESTA [fast imaging employing steady-state acquisition] or CISS [constructive interference in steady state]) sequences were reviewed on a radiology workstation. All analyzed sequences were performed without intravenous gadolinium contrast. For each sequence, the fluid signal visualized in the temporal bone was subjectively graded as either similar (isointense) or dissimilar (hyper- or hypointense) to the adjacent CSF visualized in the subarachnoid space in the same axial plane (Figure 1). Sequences were viewed as an ensemble to allow for cross-referencing and enhanced localization of the fluid on lower-resolution sequences. In the case of FLAIR sequences, where CSF is suppressed and generates minimal signal intensity, this could mean that little to no signal was seen in the mastoid, but T2-weighted sequences confirmed the presence of fluid in the mastoid at the time of the scan. FLAIR sequences were deemed isointense if fluid signal was closer to that of CSF than adjacent brain parenchyma. If there was heterogeneity in the fluid signal, sequences were graded as isointense if any portion of the fluid was judged to be isointense. Two reviewers, 1 neurotologist and 1 neuroradiologist, independently reviewed all scans. Disagreements between reviewers were adjudicated by a second neuroradiologist. Reviewers examined the scans blinded to the clinical outcome.

Radiology reports were also reviewed for commentary regarding the presence of a temporal bone encephalocele. Scans without reports mentioning the presence of an encephalocele were reviewed by the study authors, utilizing coronal and sagittal images to make this determination.

If a CSF leak was present, a sequence with an isointense effusion was considered to be a true-positive test result. Conversely, in the setting of a nonleak MEE (ie, chronic otitis media), sequences with hypo- or hyperintense effusions were considered true-negative results. Test characteristics of sensitivity and specificity were calculated in the standard fashion for each type of pulse sequence. Additionally, the positive predictive value (PPV), negative
predictive value, and overall accuracy rates were calculated for each sequence. Cohen’s kappa values were calculated for each sequence to determine levels of interrater reliability.

**Results**

Eighty effusions were included for analysis: 41 CSF leaks and 39 other MEEs. Forty patients with leaks underwent surgical repair, with 1 electing for observation despite a positive beta-2 transferrin test result. The most common indications for MRI scanning in the non–CSF leak group included evaluation of a central nervous system tumor (11 ears), evaluation of a head and neck tumor (5), suspected CSF leak (5), hearing loss (4), and chronic otitis media with concern for skull base osteomyelitis (4). T1-weighted, T2-weighted, and FLAIR sequences were available for all MRI scans; 3D T2 sequences were available for 41 studies (25 CSF leaks, 16 other MEEs), and diffusion-weighted sequences were available for 62 studies (27 CSF leaks, 35 other MEEs). The calculated values for sensitivity, specificity, PPV, negative predictive value, and overall accuracy for each pulse sequence are listed in Table 1. Details regarding true-positive, true-negative, false-positive, and false-negative rates are reported in Table 2.

Most notably, FLAIR and 3D T2 pulse sequences both demonstrated 100% specificity and PPV. Stated differently, if an effusion was judged to have signal isointense to surrounding CSF on either of these sequences, this was always predictive of a CSF leak. Sensitivity for detection of CSF leak was 44% for FLAIR and 76% for 3D T2.

Standard T1-weighted, T2-weighted, and diffusion-weighted imaging demonstrated less favorable test characteristics. Higher sensitivity was generally marred by lower specificity. On standard thick-section T2-weighted sequences in particular, a high false-positive rate was seen, as essentially all effusions (77 of 80) were deemed isointense to surrounding CSF.

### Table 1. Test Characteristics for MRI Pulse Sequences in Detecting CSF Leak.\(^a\)

<table>
<thead>
<tr>
<th>Sequence</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>80</td>
<td>73</td>
<td>69</td>
<td>71</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>T2</td>
<td>80</td>
<td>97</td>
<td>5</td>
<td>52</td>
<td>67</td>
<td>53</td>
</tr>
<tr>
<td>FLAIR</td>
<td>80</td>
<td>44</td>
<td>100</td>
<td>100</td>
<td>63</td>
<td>71</td>
</tr>
<tr>
<td>3-dimensional T2</td>
<td>41</td>
<td>76</td>
<td>100</td>
<td>71</td>
<td>73</td>
<td>85</td>
</tr>
<tr>
<td>Diffusion weighted</td>
<td>75</td>
<td>63</td>
<td>66</td>
<td>59</td>
<td>70</td>
<td>64</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value.

\(^a\)Values are presented as percentages unless noted otherwise.

### Table 2. Results for Each MRI Pulse Sequence: True/False Positive and Negative.\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>CSF Leak</th>
<th>Other MEE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>True positive</td>
<td>False positive</td>
</tr>
<tr>
<td>Hyper-/hypointense</td>
<td>False negative</td>
<td>True negative</td>
</tr>
<tr>
<td>T1 (N = 80)</td>
<td>30 (38)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Isointense</td>
<td>11 (14)</td>
<td>27 (34)</td>
</tr>
<tr>
<td>Hyper-/hypointense</td>
<td>40 (50)</td>
<td>37 (46)</td>
</tr>
<tr>
<td>T2 (N = 80)</td>
<td>19 (46)</td>
<td>0</td>
</tr>
<tr>
<td>Isointense</td>
<td>23 (29)</td>
<td>39 (49)</td>
</tr>
<tr>
<td>Hyper-/hypointense</td>
<td>6 (15)</td>
<td>16 (39)</td>
</tr>
<tr>
<td>FLAIR (N = 80)</td>
<td>17 (27)</td>
<td>12 (19)</td>
</tr>
<tr>
<td>Isointense</td>
<td>10 (16)</td>
<td>23 (37)</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; MEE, middle ear effusion; MRI, magnetic resonance imaging.

\(^a\)Values are presented as n (%).
Of the 41 CSF leaks, 13 had radiographic evidence of an encephalocele. Among these 13 cases, FLAIR sensitivity for detection of CSF leak was 53% (7 of 13), while 3D T2 sensitivity rose to 100% (7 of 7). These differences in sensitivity did not reach statistical significance when compared with the group without radiographic encephalocele ($P = .38$ for FLAIR, $P = .080$ for 3D T2). Operative reports confirmed an encephalocele of any size during 29 (of the 40) CSF leak repairs, including all those with radiographically evident encephaloceles.

Cohen’s kappa, a statistical measure of interrater agreement, varied with each sequence between the primary 2 raters. The strongest agreement was seen with 3D T2 interpretation, where reviewers agreed on 76% of scans ($\kappa = 0.527$), followed by T1 (73%,$\kappa = 0.47$), FLAIR (79%,$\kappa = 0.258$), diffusion weighted (43%, $\kappa = 0.241$), and standard T2 (76%, $\kappa = 0.033$). Kappa values between 0.41 and 0.60 are generally considered to indicate moderate agreement; 0.21 to 0.40, fair agreement; and 0.0 to 0.2, slight agreement.

**Discussion**

We found that subjective comparison of mastoid or middle ear fluid with CSF visualized on MRI scans was a highly specific and fairly sensitive means to identify cases of temporal bone CSF leak. The FLAIR and 3D T2 pulse sequences provided the overall best diagnostic accuracy. The demonstrated high specificity (good “rule-in” ability) suggests that data obtained from MRI scanning are useful in the decision-making process before undertaking surgical repair.

Not infrequently, patients will be referred to the otologist for an incidental imaging finding of fluid within the mastoid. Most present without symptoms of acute otitis/mastoiditis, and the only relevant clinical findings might be a visualized MEE and some degree of conductive hearing loss. The present work was partially motivated by the desire to obtain as much information as possible from the MRI scan alone in this clinical scenario.

In cases with typical CSF leak presentations, the diagnosis can be straightforward for experienced clinicians. Hallmark signs and symptoms include clear rhinorrhea, salty or metallic-tasting postnasal drainage, or continuous otorrhea in the case of a coincident tympanic membrane (TM) defect. Elevated body mass index or evidence of high intracranial pressure may heighten suspicion. Many will present to an otologist for high-volume clear drainage that persists after a tympanostomy tube placement. Leaks are rarely identified after patients present with meningitis.4

Beta-2 transferrin (less commonly, beta-trace) protein testing is the gold standard means to detect CSF contamination within a body fluid.1,5 If the fluid is readily available from a draining ear, beta-2 testing is a simple option to confirm the diagnosis before embarking on treatment. However, when a patient presents with an intact TM and there is no collectable fluid leaking into the nose, these fluid assays require a myringotomy. In addition to the risks of a persistent perforation requiring repair, myringotomy with or without tympanostomy tube placement may lead to troublesome ongoing drainage if a high-flow leak is present.

For many surgeons, including those at our institution, MRI scanning is part of the standard preoperative evaluation before embarking on CSF leak repair. MRI can evaluate for encephaloceles, assess adjacent intracranial anatomy, and reveal indirect indicators of elevated intracranial pressure that may mandate more active management, such as an empty sella, distended optic sheaths, and posterior globe flattening.6

There are many imaging techniques that are utilized to suggest or confirm the presence of CSF leaks. Computed tomography (CT) scans can demonstrate small tegmen defects, and if a protruding soft tissue density (encephalocele) is seen in association with the defect, the diagnosis is strongly suggested.7 MRI has superior soft tissue resolution for delineation of encephaloceles, although its ability to localize bony defects is limited. The imaging techniques are considered complimentary in making an accurate diagnosis and precise localization of the leak.

The utility of MRI alone in diagnosing CSF leaks and encephaloceles extending from the anterior skull base was shown in series of patients undergoing surgical repair, with the authors paying attention to encephaloceles and hyperintense T2 signal in continuity between the intracranial space and the nasal cavity or sinuses.8 High-resolution and heavily T2-weighted 3D CISS imaging (sometimes referred to as magnetic resonance cisternography) was also demonstrated as being sensitive in locating anterior and lateral skull base CSF leaks in populations undergoing surgical repair.9,10 Fluid with hyperintense T2 signal and low FLAIR signal was previously reported as being compatible with CSF leakage, arachnoid granulations, and petrous apex cephaloceles.11-13 These case series report findings were consistent with ours, although we believe our work to be novel in the demonstration of high specificity in the general population of patients with indeterminate MEEs.

We should mention that CT cisternography or intrathecal radionuclide studies are means to absolutely confirm continuity between the intracranial space and the temporal bone, although they require a lumbar puncture with its attendant potential complications. As 3D T2 imaging techniques have been demonstrated to be more sensitive than CT cisternography, we cannot recommend the routine use of such procedures in the evaluation of CSF leaks.9

Our finding of 100% specificity and PPV for CSF leak with isointense effusions on FLAIR or 3D T2 is of significant clinical utility. If an isointense effusion is seen on either of these sequences, the diagnosis can be made with a high degree of confidence even without confirmatory beta-2 testing. Adjunctive clinical data, such as a temporal bone encephalocele on MRI, a recent history of skull base surgery or trauma, clear rhinorrhea, or visualization of an atypically crystal-clear effusion on examination may further secure the diagnosis.

FLAIR and T2-weighted imaging are able to grossly assess the molecular composition of a given fluid.3 FLAIR
in particular was shown to be sensitive to varying protein levels within CSF, and we suspect that this property makes it useful in identification of CSF leaks. The 3D T2 sequences utilize heavier T2 weighting and demonstrate higher signal-to-noise ratios when compared with conventional 2D T2-weighted imaging.\textsuperscript{14} This is likely to be the mechanism by which finer differentiation among various fluids on 3D T2 was made possible in the present study. With conventional T2 imaging, all fluids (effusion or CSF) appeared very bright, making differentiation difficult.

The ability of MRI to assess fluid composition was demonstrated clinically in the diagnosis of vestibular schwannoma, as fluid signal within the cochlea or the "fundal cap" lateral to the intracanalicular tumor component can become distinct from the surrounding CSF on MRI.\textsuperscript{15-18} This is thought to be related to known increases in inner ear fluid protein content that develop in the presence of the tumor.\textsuperscript{19-21} We theorize that a similar change in the effusion content occurs with stasis in the temporal bone, leading to the observed imaging findings with MEEs related to chronic otitis media. In cases of a slower-flow CSF leak (impaired eustachian tube function, intact TM), the fluid may take on imaging characteristics similar to those of MEEs seen with chronic otitis media. This is congruent with our finding of multiple false negatives (ie, missed leaks) when fluid signal intensity was utilized as a detection method. We sought to minimize these false negatives by grading effusions as isointense if any component of the fluid, though not necessarily the entire effusion, appeared isointense to adjacent CSF. The fluid within the antrum, epitympanum, and middle ear would expect to be turned over at a higher rate as it flows from the tegmen defect out through a patent eustachian tube or TM perforation. The fluid in the mastoid tip would likely be more static, mix with serous fluid, and be less likely to retain imaging characteristics of CSF. Additionally, the largest contiguous spaces without bony partitions (ie, the antrum and middle ear space) tended to be the subjectively clearest anatomic regions for assessing the middle ear fluid on the scans. Despite our study protocol, a somewhat high false-negative rate persisted for most sequences, making MRI a less valuable screening method for leaks. Therefore, if the clinical scenario still suggests a leak even with MRI suggesting a non-CSF effusion, confirmatory beta-2 testing or proceeding to surgical exploration/repair would likely be prudent.

We acknowledge multiple relative weaknesses of our study. Primarily, the subjective nature of grading the scans limits the generalizability of the findings. Objective or quantitative means of measuring signal intensity of fluid were considered, but these techniques may also have inherent bias or subjectivity. In particular, the selection of the region of interest is not necessarily an objective task and can be limited by scan resolution or distribution of the fluid. Our more subjective and binary classification system is more easily applied by the physician in a clinical setting, although experience in MRI interpretation undoubtedly plays a role in the utility of this technique. Reviewers also examined all MRI sequences as a complete data set, rather than looking at each sequence in isolation. The rationale for this was to help the reviewer utilize higher-resolution sequences to localize the middle ear, mastoid antrum, or other locations harboring larger volumes of fluid on the lower-resolution sequences. Position data are typically encoded into the images, allowing for cross-referencing between sequences. However, it is certainly possible that interpretation of the fluid signal characteristics on one sequence influenced the reviewer's judgement on other sequences. Additionally, a visualized encephalocele could raise the reviewer's suspicion that a leak was present. Confirmation bias could then lead to a judgment that an indeterminate fluid appeared isointense, as the reviewers were aware of the purpose and rationale for the study. We attempted to minimize this effect by examining only axial sequences when analyzing fluid signal. Coronal and sagittal sequences were examined separately to assess an encephalocele. The rate of CSF leak detection did not significantly improve among patients with radiographically evident encephaloceles, although there was a trend toward this on 3D T2 sequences.

The agreement between the primary reviewers was fair for this study, demonstrating the subjective nature of scan interpretation. Interestingly, all cases of disagreement for FLAIR (17 of 80) or 3D T2 (10 of 41) were cases of CSF leaks (false negatives), although the same reviewer correctly identified all of these leaks. While a higher rate of agreement would be preferable, this does highlight the high specificity of this method.

The current data do not support MRI scanning to screen all patients with a simple-appearing MEE and no other clinical findings to suggest CSF leak. In light of the relatively low incidence of spontaneous CSF leaks, the high cost of an MRI scan, and the low morbidity of a myringotomy, this is unlikely to be a viable strategy for efficient patient care. However, we advocate for the full utilization of available MRI scan data by assessing effusion signal characteristics on FLAIR and 3D T2 sequences.

We wish to highlight multiple avenues for future study. Quantitative evaluation of fluid signal intensity in the middle ear or mastoid will be further explored, decreasing subjectivity of scan interpretation and improving generalizability of the findings. Performing a similar study with a large patient population and additional reviewers would help better define the test characteristics as well as better understand interrater reliability via our methods. The present work evaluated only the signal intensity for each sequence in isolation to detect CSF leaks. However, by taking into account anatomic factors or visualized pathology such as encephalocele, evidence of intracranial hypertension, or obstructive central skull base/nasopharyngeal pathology, an even more sensitive or specific test/rule could be developed from the complete data set given by each scan. Finally, we evaluated only cases of spontaneous CSF leakage. While we would anticipate that these findings would extend to evaluation of traumatic or iatrogenic leaks after skull base surgery, this claim would need to be substantiated.
Conclusion
MRI scan protocols utilized in routine practice, specifically FLAIR and 3D T2 pulse sequences, have significant utility in differentiating CSF leaks from other effusions within the temporal bone. Previous work demonstrated that signal intensity on FLAIR and 3D T2 imaging is sensitive to fluid protein content, and this is the presumed mechanism by which the scan can differentiate types of effusion. Stasis of CSF that leaks into the temporal bone but does not rapidly leak out the eustachian tube or TM is a possible cause for false-negative scans that did not detect CSF leaks. Despite this weakness, high specificity and PPV for detection of CSF leak were demonstrated, highlighting the use of MRI as a rule-in test that may obviate confirmatory beta-2 transferrin testing before proceeding to surgical repair.

Author Contributions
Joseph T. Breen, conception and design of work, acquisition of data, analysis and interpretation of data, drafting of manuscript, approval of final version; Colin R. Edwards, conception and design of work, acquisition of data, analysis and interpretation of data, drafting of manuscript, approval of final version; Rebecca S. Cornelius, design of work, acquisition of data, analysis and interpretation of data, drafting of manuscript, approval of final version; Gavriel D. Kohlberg, design of work, analysis and interpretation of data, drafting of manuscript, approval of final version; Ravi N. Samy, design of work, analysis and interpretation of data, drafting of manuscript, approval of final version; Myles L. Pensak, design of work, analysis and interpretation of data, drafting of manuscript, approval of final version.

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References