REVIEW

The Technical and Clinical Features of 3D-FLAIR in Neuroimaging

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In clinical MR neuroimaging, 3D fluid-attenuated inversion recovery (3D-FLAIR) with a variable-flip-angle turbo spin echo sequence is becoming popular. There are more than 100 reports regarding 3D-FLAIR in the PubMed database. In this article, the technical and clinical features of 3D-FLAIR for neuroimaging are reviewed and summarized. 3D-FLAIR allows thinner slices with multi-planar reformation capability, a higher flow sensitivity, high sensitivity to subtle T_1 changes in fluid, images without cerebrospinal fluid (CSF) inflow artifacts, and a 3D dataset compatible with computer-aided analysis. In addition, 3D-FLAIR can be obtained within a clinically reasonable scan time. It is important for radiologists to be familiar with the features of 3D-FLAIR and to provide useful information for patients.

Keywords: *magnetic resonance imaging, endolymphatic hydrops, 3D-FLAIR*

Introduction

Fluid-attenuated inversion recovery (FLAIR) images are widely utilized in neuroimaging. Suppression of the cerebrospinal fluid (CSF) signal makes the recognition of various pathologies near the CSF space easier.^{1,2} 2D-FLAIR is used most often as part of routine clinical studies. 3D-FLAIR enables the acquisition of thinner slices without a significant CSF ghost artifact.^{3,4} The three-dimensional dataset obtained by 3D-FLAIR has the potential to be evaluated by computer-assisted quantitative post-processing analyses.^{5,6} Recent technical developments have shortened the acquisition time for 3D-FLAIR, facilitating use in a routine clinical setting as well as in specific clinical applications. Now, more than 100 papers can be found by a PubMed search for “3D-FLAIR”. In this review, the technical features and clinical applications of 3D-FLAIR are reviewed and summarized for those who employ 3D-FLAIR imaging in clinical practice.

Technical Features

2D-FLAIR

2D-FLAIR was initially obtained using a conventional spin echo sequence. Despite a longer scan time, better lesion conspicuity by 2D-FLAIR was expected, promising application to a wide range of diseases.⁷ Single-shot echo planar imaging (ss-EPI)-based 2D-FLAIR was reported to shorten the scan time dramatically; however, image distortion and low spatial resolution limited its utility.⁸ By utilization of a fast spin echo sequence, 2D-FLAIR came into routine clinical practice.²

2D vs 3D

To acquire thinner slices, 3D acquisition is preferable, although 3D acquisition increases the scan time compared to 2D acquisition. In 2D-FLAIR, especially with thinner slices, CSF inflow artifacts can be a problem.^{3,4} FLAIR can sensitively detect subarachnoid hemorrhage (SAH); however, CSF artifacts can cause false-positive findings.⁹ 3D-FLAIR allows the suppression of CSF-related artifacts as well as retrospective multi-planar slice reformatting (Fig. 1).^{3,10,11} One pitfall of 3D-FLAIR is the frequently obscured ivy sign in moyamoya disease.¹² Another pitfall of 3D-FLAIR is less visibility for intra-arterial hyperintensity in patients

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Fig. 1. Comparison of CSF-related artifacts on 2D- and 3D-FLAIR. 3D-FLAIR images are reformatted to 4.5 mm thick, which are identical to the 2D-FLAIR images. At the lateral-ventricle-level slice, CSF pulsation artifacts aligned in the phase encoding direction are seen on 2D-FLAIR (**a**) (arrows), but not on 3D-FLAIR (**b**). At the pons level, a CSF inflow artifact is seen on 2D-FLAIR (**c**) (arrows), but not on 3D-FLAIR (**d**).

with acute ischemic stroke (Fig. 2).¹³ In contrast, 2D-FLAIR sometimes suffers from an incomplete inversion pulse effect in areas disturbed by metallic substances.¹⁴ In a single-slab 3D-FLAIR covering the whole brain, a thicker inversion pulse or a non-spatially selective inversion pulse is utilized. Artifacts caused by metallic substances are usually weaker with 3D-FLAIR than with 2D-FLAIR (Fig. 3).¹⁴

Single slab or multi-slab

To cover the whole brain with a single slab, more than 160 slices are usually required. Using a conventional turbo spin echo (TSE) sequence with an echo train length (ETL) of around 30, scan time can exceed 1 h. A multi-slab approach using a conventional TSE sequence improves the time efficiency. During the repetition time period, multiple slabs are excited sequentially. To acquire gapless slices, it is necessary to obtain more than two separate sets

of interleaved multi-slabs. This requirement reduces the time efficiency. The multi-slab approach is a hybrid of 2D and 3D acquisitions, but multi-slab 3D-FLAIR is not currently used widely in clinical applications due to the slab boundary artifact in reformatted images.¹⁵

To shorten the scan time of single-slab 3D-FLAIR, a variable-flip-angle turbo spin echo (VFA-TSE) sequence is usually employed.^{14–16} In this review, 3D-FLAIR by VFA-TSE is mostly discussed.

Variable-flip-angle turbo spin echo

To shorten the scan time in TSE imaging, increasing the echo train length is one solution. To suppress the blurring of anatomical details, the echo spacing should be kept as short as possible. To achieve a short echo spacing, a non-spatially selective radio-frequency (RF) pulse can be used. Furthermore, to suppress blurring from the T_2 decay of the late echo, a reduced flip angle of refocusing RF

Fig. 2. A 71-year-old woman with cerebral infarction

In the 2D-FLAIR image, arterial hyperintensity in the branch of the anterior and middle cerebral arteries with slow flow is visualized (**a**) (arrows). These high signals are not visible in the 3D-FLAIR image (**b**) (arrows).

Fig. 3. A 62-year-old man with metal dental materials

Severe artifact is seen in the sagittal T₁-weighted image (**a**) (arrow). In the 2D-FLAIR image, signal increase of CSF in the frontal subarachnoid space mimics subarachnoid hemorrhage (**b**) (arrows). This is probably due to incomplete inversion of CSF in the frontal area by the presence of a metallic object. In 3D-FLAIR with non-selective inversion recovery pulse, CSF in the frontal area is properly suppressed (**c**) (arrows).

pulses should be utilized.¹⁵ The reduced flip angle in refocusing RF pulses stores the magnetization in the longitudinal direction, thereby avoiding the quick T₂ decay. This utilizes the fact that the T₁ relaxation time is far longer than the T₂ relaxation time. By refocusing the RF pulses with variable flip angles, the stimulated echo contributes to the signals during the echo train. Thus, a very long echo train length can be used in practical terms (Fig. 4). VFA-TSE has vendor-specific names such as SPACE (sampling perfection with application optimized contrasts using different flip-angle evolution; Siemens), Cube (GE), and VISTA (volume

isotropic turbo spin echo acquisition; Philips).^{14,15}

Flow sensitivity

The reduced refocusing flip angle of the VFA-TSE cannot rephase the flowing spins as a 180° pulse does. The sensitivity to flow is higher in a VFA-TSE than in a conventional TSE.^{12,14} The lack of a vessel signal (usually from velocities over 1 cm/s) in 3D-FLAIR¹² makes the recognition of subarachnoid pathologies easier by the suppression of vascular and CSF signals; however, an obscured high-intensity vessel sign in acute stroke cases¹³ or an unclear ivy sign in moyamoya disease¹² cases

can be problematic.

Slab-selective excitation

Although non-selective slab excitation and signal reception by a hard RF pulse allow for reduced echo spacing and increased scan efficiency, some clinical applications such as inner ear imaging need slab-selective excitation to achieve a high resolution while keeping the scan time within a clinically acceptable level. Slab-selective excitation can be performed using an excitation RF pulse that is spatially selective in one or more dimensions.^{15,17} In a VFA-TSE sequence, a relatively long echo spacing is used for the first echo to accommodate the long slab-selective excitation pulse, while a short echo spacing is used for the second and subsequent ech-

Fig. 4. Schematic plots of flip angles for refocusing RF pulses in conventional turbo spin echo (TSE) and variable flip angle TSE

In conventional TSE, constant 180° pulses are utilized (straight line). In VFA-TSE, an initial flip angle ramp is followed by less than 180° (dotted line). This curve is an example. The optimal curve shape of this graph is different among the tissues with different T_1 and T_2 values.

oes.¹⁵ To suppress the out-of-slab FID artifacts, partial averaging of more than 1.4 is usually employed.¹⁵

T_2 -selective inversion recovery

The scan time of a single-slab 3D-FLAIR tends to be long even with a VFA-TSE, but it can be shortened using the slab-selective excitation described above. In addition, there are other ways to further shorten scan time. Partial Fourier imaging and parallel imaging are routinely applied solutions. Shortening of the repetition time (TR) is another. Usually, a long TR (usually more than 8 s at 3T) is necessary to sufficiently suppress the signal from the CSF while keeping the adequate signal-to-noise ratio of the brain.¹⁸ To shorten the TR, T_2 -selective inversion recovery (IR) has been proposed. In this method, the inversion pulse is replaced with a $90(x)$ - $180(y)$ - $90(x)$ preparation sequence that provides T_2 selectivity. This allows the magnetization of the tissue with a shorter T_2 to recover more rapidly than the CSF with a longer T_2 , permitting the use of shorter TR values.¹⁹

The $90(x)$ - $180(y)$ - $90(x)$ pulses are more susceptible to local magnetic inhomogeneities than regular inversion pulses. The residual fluid signal near the bone and air (such as the labyrinthine fluid) is observed as artifacts (Fig. 5). At 7T, implementation of the FLAIR sequence is difficult as the increased T_1 weighting from the prolonged T_1 constants dominates the desired T_2 contrast and yields a suboptimal signal-to-noise ratio. Magnetization preparation for 3D-FLAIR has been used at 7T to reduce the T_1 weighting and improve the T_2 weighting.²⁰ There is another way to shorten the TR of a 3D-FLAIR. A shorter TR can be applied in the peripheral part of the k -space while smoothly modulating TR and TI throughout the k -space. Scan time can be reduced effectively by this approach,

Fig. 5. A 3D-FLAIR image by conventional inversion recovery pulse (a) and that by T_2 -selective inversion recovery pulse (b) at 3T

The repetition time is 9,000 ms for (a) and 5,000 ms for (b). The fluid shows a high signal in (b) at the area near the air or bone due to an imperfect inversion by field inhomogeneity (arrows). Long arrows indicate the cerebellopontine angle cistern, and short arrows indicate the lateral part of the vestibule. A T_2 -selective inversion recovery pulse is more susceptible to local magnetic field inhomogeneities than a regular inversion recovery pulse.

Fig. 6. A 60-year-old man with sudden deafness in the right ear

(a) CISS image, (b) non-contrast-enhanced 3D-FLAIR, and (c) non-contrast-enhanced T_1 -weighted image. Lymph fluid in the right cochlea (long arrow) and right vestibule (short arrow) show increased signal on 3D-FLAIR imaging compared to the other side. This is presumed to be due to an increased protein concentration or slight hemorrhage in the right labyrinth. A signal increase in the right labyrinth cannot be detected on the T_1 -weighted image.

while keeping the contrast-to-noise ratio similar to a constant TR sequence.¹⁸

High sensitivity to subtle T_1 changes in fluid

FLAIR is reported to be more sensitive to subtle T_1 changes in fluid than conventional T_1 -weighted images.^{21–30} A FLAIR image allows the detection of subtle subarachnoid hemorrhage in the CSF space,⁹ signal increases in CSF after the inhalation of oxygen,³¹ and subtle compositional changes of the labyrinthine fluid (Figs. 6 and 7),^{26,27,30,32–34} which can be difficult to recognize on T_1 -weighted images. Heavily T_2 -weighted 3D-FLAIR has been reported to be much more sensitive than regular-contrast 3D-FLAIR.³⁵ After intravenous administration of a single dose of gadolinium-based contrast media (IV-SD-GBCM), a signal increase in various fluid spaces such as the anterior eye segment, optic nerve sheath, Meckel's cave, ambient cistern, internal auditory canal, and perilymph of the labyrinth has been reported.^{36–39}

Prospective motion correction

The scan time for a 3D-FLAIR is usually several minutes to 15 min. Patient motion during the scan results in blurring of the images. Fortunately, there are “dead” periods without RF pulses and gradient activities while waiting for the signal recovery during the long TR of a single-slab 3D-FLAIR. Thus, there is enough time to insert an EPI-based navigator scan at every TR. This approach can update the position and orientation of the slab and avoid the spin history effect that cannot be eliminated by retrospective motion correction.⁴⁰

Local excitation by parallel transmission

An advanced slab-selective excitation technique has been introduced recently. Inner-volume imaging using a three-dimensional parallel spatially selective excitation allows for reduced field-of-view imaging of selectively excited targets. This produces a higher spatial resolution and significantly reduced measurement times *in vivo*. This approach is useful for a reduction of the distortion in EPI-based diffusion-weighted images, as well as a reduction in the blurring artifacts on VFA-TSE.⁴¹

Clinical Applications

Multiple sclerosis

FLAIR is useful for the evaluation of pathologies near or in the fluid space. For 3D-FLAIR, there are many reports regarding application to multiple sclerosis.^{5,6,42–54} Smaller lesions can be detected by 3D-FLAIR than by 2D-FLAIR due to thinner slices and fewer flow artifacts with 3D-FLAIR.^{45,46} Excellent detection of cortical lesions by 3D-FLAIR has also been reported (Fig. 8).^{43,44} Cortical lesions are rather specific for multiple sclerosis (MS), and they occur in the earliest stages of the disease.⁵⁰ It is clinically important to make cortical lesions visible *in vivo* by clinical 3D MR imaging. At both 1.5 and 3T,^{48,55} double inversion recovery (DIR) sequence is more sensitive in detecting cortical lesions than 3D-FLAIR; however, 3D-FLAIR is reported to be more sensitive than DIR at 7T.⁵⁰ In the present clinical setting, 3D-FLAIR is one of the important multi-contrast pulse sequences to evaluate cortical lesions. Computer-based quantitative evaluation can be applied to 3D-FLAIR by the reduction of partial volume averaging effects.^{5,6} MS lesions usually follow a perivascular orientation. Typical MS lesions run along the veins that stretch from the lateral ventricles into the brain.⁵⁰ Perivascular lesion orientation can be appreciated on 3D-FLAIR for MS lesions by combining with T_2^* -weighted imaging.⁵⁰ A combination of 3D-FLAIR

Fig. 7. A 43-year-old man with a right labyrinthine fistula from a cholesteatoma (a) CISS image, (b) non-contrast-enhanced 3D-FLAIR, (c) non-contrast-enhanced T₁-weighted image, and (d) CT image of the right side. Lymph fluid in the right cochlea (long arrow) and right vestibule (short arrow) shows an increased signal on 3D-FLAIR imaging compared to the other side. This is presumed to be due to an increased protein concentration or slight hemorrhage in the right labyrinth by invasion of a cholesteatoma. A signal increase in the right labyrinth cannot be detected on the T₁-weighted image. (d) A fistula to the lateral semi-circular canal from a cholesteatoma is visualized (black arrow).

and susceptibility-weighted imaging (SWI) or T₂*-weighted imaging is useful for the assessment of perivascular lesions.^{50,56}

Cerebrovascular disease

3D-FLAIR allows FLAIR imaging with virtually no CSF artifacts and is, thus, particularly useful for SAH detection (Fig. 9).⁹ Lack of visualization for intra-arterial signal in the patients with acute ischemic stroke in 3D-FLAIR is one of the drawbacks.¹³

Cortical microinfarcts (CMIs) are detected as small foci restricted to the cerebral cortex in autopsy brains. CMIs are thought to be caused by cerebral amyloid angiopathy in the elderly and may be a risk for dementia. It has been reported that CMIs can be detected by 3D-FLAIR and DIR at 3T.⁵⁷ High-signal-intensity abnormalities within the drainage territory of developmental venous anomalies were also observed on 3D-FLAIR around vascular structures.⁵⁶

Meningeal pathologies

Due to a higher sensitivity to subtle compositional changes from fluid and a reduced incidence

of artifacts from CSF motion, post-contrast 3D-FLAIR is valuable for the evaluation of various kinds of meningitis.^{21,58,59} On post-contrast 3D-FLAIR images, enhancement in the fundus of the internal auditory canal (IAC) was frequently observed in patients with meningeal disease, even at 10 min after administration of the contrast agent. This enhancement in the IAC fundus is not discernable on T₁-weighted 3D-FLASH images.⁵⁸ The rim patterns of intracranial meningiomas on non-enhanced 3D-FLAIR images were reported to be useful to predict surgical cleavability and for histological tumor grading.⁶⁰

Visualization of white matter tracts

For the visualization of neuronal white matter tracts, diffusion tensor imaging (DTI) is widely used. DTI is usually performed with single-shot echo planar imaging, which is susceptible to distortion. On non-contrast-enhanced 3D-FLAIR, the brainstem tracts can be delineated and correlated with DTI results.⁶¹ More conspicuous tract visualization has been reported by non-contrast-enhanced heavily T₂-weighted 3D-FLAIR. Distortion-free,

volumetric image presentation of tracts is also possible by non-contrast-enhanced heavily T₂-weighted 3D-FLAIR (Fig. 10).⁶²

Fig. 8. A 38-year-old woman with multiple sclerosis. A cortical lesion in the left frontal lobe cortex is visualized in the 1-mm-thick 3D-FLAIR image (a) (arrow), but the precise location of this lesion is unclear in the 4.5-mm-thick 2D-FLAIR image (b) (arrow). In the lower level slice, no cortical lesion is seen around the Sylvian fissure in the 1-mm-thick 3D-FLAIR image (c) (arrow); however, a high-signal artifact in CSF mimics a cortical lesion in the 4.5-mm-thick 2D-FLAIR image (d) (arrow).

Signal change in the labyrinthine fluid

Sudden deafness

In ears with sudden deafness, labyrinthine fluid signal increase is frequently observed on 3D-FLAIR, but not on T₁-weighted 3D gradient echo images.^{32,63} An increased contrast enhancement of the labyrinthine fluid on 3D-FLAIR is sometimes observed in ears with sudden deafness after an intravenous administration of a gadolinium-based contrast material.^{32,64} This contrast enhancement suggests the breakdown of the blood-labyrinthine barrier.⁶³ Prognosis for hearing was not good in ears with a high signal on precontrast 3D-FLAIR.^{65,66}

Inflammation

A signal increase in the labyrinthine fluid on 3D-FLAIR in various inflammatory diseases such as acute meningitis, acute otitis media, Wegener's granulomatosis,²⁷ mumps deafness,²⁶ Ramsay-Hunt syndrome,^{67–69} and labyrinthine fistula by a cholesteatoma⁷⁰ has been reported. Signal increase in the labyrinthine fluid on precontrast 3D-FLAIR suggests the presence of a small degree of hemorrhage or protein, and on post-contrast 3D-FLAIR, enhancement of the labyrinthine fluid suggests the active breakdown of the blood-labyrinthine barrier.^{27,30}

Vestibular schwannoma

A signal change of the labyrinthine fluid on 3D-FLAIR was also observed in ears with vestibular schwannoma.⁷¹ The results of this study suggested that an alteration of cochlear fluid composition and an increased permeability of the blood-labyrinthine barrier existed in the affected side in patients with vestibular schwannoma. Furthermore, although weak, a positive correlation between the post-con-

Fig. 9. A 56-year-old woman with hypertension and severe headache. Subtle subarachnoid hemorrhage in the sulcus is unclear in the 5-mm-thick 2D-FLAIR image (a) (thin arrows) but can be recognized on the 1-mm-thick 3D-FLAIR image (b) (thin arrows). Note that ghost artifact from the superior sagittal sinus (a) (short arrows) and chemical shift artifact in the slice-select direction by fatty marrow of the inner table (a) (bold arrows) overlap the surface of the brain. These artifacts in 2D-FLAIR make the recognition of subtle subarachnoid hemorrhage further difficult.

Fig. 10. Non-diffusion-based tractography

A thin-slab maximum intensity projection image (5 mm thick) of a heavily T_2 -weighted 3D-FLAIR image of the brain in a healthy subject. **(a)** Coronal projection image. The corticospinal tract (arrows) is visualized on both sides. **(b)** Oblique sagittal projection image. The corticospinal tract (arrow), medial lemniscus (dotted arrows), and superior cerebellar peduncle (short arrows) are clearly visualized. Note that there is no distortion artifact as seen on EPI-based DTI tractography.

trast cochlear signal intensity on 3D-FLAIR and hearing level was observed. The cochlear signal on 3D-FLAIR may be useful as an additional parameter when monitoring the degree of functional impairment during follow-up of patients with a small vestibular schwannoma confined to the internal auditory canals.⁷² Incidentally, endolymphatic hydrops can be recognized on non-contrast-enhanced 3D-FLAIR images due to the signal increase of the perilymph.³³

Endolymphatic hydrops

Visualization of endolymphatic hydrops (EH) in patients with Ménière's disease was first achieved using 3D-FLAIR obtained at 24 h after intratympanic administration of GBCM (IT-GBCM).²⁵ Enhancement of the perilymph was not found on T_1 -weighted 3D gradient echo images. Numerous reports have been published using IT-GBCM.^{24,29,73–95} The IT-GBCM method opens the possibility for an objective diagnosis of Ménière's disease. The relationship between EH and symptoms is under investigation. However, there are some drawbacks to the IT-GBCM method. One is that the IT administration is an off-label use of GBCM. A second drawback is that the GBCM penetration of the round window membrane is insufficient to visualize EH in nearly 20% of patients.⁸⁹ Third, 24 h of waiting time is needed after the administration of GBCM before starting the MR imaging.²⁴ The final drawback is that only the injected ear can be evaluated. One advantage of IT-GBCM is the capability for simulation of the intralabyrinthine distribution of the intratympanically administered drug.⁹⁶ Although IT-GBCM was usu-

ally performed through the tympanic membrane, some researchers administered the GBCM through the Eustachian tube.⁹⁷

To decrease the invasiveness of IT-GBCM, evaluation of EH by intravenous administration of GBCM (IV-GBCM) was tried. A combination of double-dose IV-GBCM and 3D-FLAIR imaging enabled the visualization of EH.^{98–100} Usually, 4 h after IV-GBCM, MR imaging can be conducted.

To further decrease the invasiveness, a single dose of IV-GBCM and heavily T_2 -weighted 3D-FLAIR enabled the visualization of EH.³⁹ By the development of a single-dose IV-GBCM method, the imaging evaluation of EH became clinically feasible, and various studies using this method have been reported (Fig. 11).^{37,38,101–108}

In summary, 3D-FLAIR using VFA-TSE has several unique advantages for clinical neuroimaging as shown below:

- 1) Thinner slices and multi-planar reformation capability,
- 2) Higher flow sensitivity,
- 3) High sensitivity to subtle T_1 changes in fluid,
- 4) Free from CSF inflow artifacts,
- 5) Reasonable scan time, and
- 6) A 3D dataset that allows computer-aided analysis.

Familiarity with these features of 3D-FLAIR imaging and proper use of 3D-FLAIR are important in order for radiologists to obtain useful information for patient management.

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Fig. 11. A 73-year-old man with right Ménière's disease
(a) An MR cisternographic image (MRC) and **(b)** a heavily T_2 -weighted 3D-FLAIR image obtained 4 h after intravenous administration of a single dose of a gadolinium-based contrast material. The perilymph shows high signal in this positive perilymph image (PPI). **(c)** A positive endolymph image (PEI) obtained by a shortening of the inversion time of the PPI. **(d)** The subtraction image of the PEI from the PPI (HYbrid of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal, HYDROPS) provides an image that can be easily interpreted. The long arrows indicate a significantly dilated endolymphatic space in the right cochlea. The short arrow indicates a significantly dilated vestibular endolymphatic space. **(e)** Subtraction of the MRC from the PPI provides a similar contrast appearance image as **(d)**. This image is called a HYDROPS2 image. A HYDROPS2 (HYbrid of Reversed image Of MR cisternography and positive Perilymph Signal by heavily T_2 -weighted 3D-FLAIR) image can be obtained in a shorter scan time than a HYDROPS image.

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