UCSF-QUEST DIAGNOSTICS PARTNERSHIP
DEMENTIA CARE PATHWAYS

RADIOLOGIST MRI INTERPRETATION MANUAL

A. BACKGROUND

Most clinical neurology practice guidelines in North America recommend imaging as an integral part of the initial evaluation of patients presenting with cognitive complaints.[1] Until recently, the basis for this recommendation has been to identify structural lesions associated with dementing illnesses, such as tumors, hydrocephalus and hemorrhage. Although imaging still plays an important exclusionary role in this context, fewer than 5% of studies reveal an unsuspected but clinically significant structural lesion.

There has been a recent push to increase the diagnostic role for neuroimaging in patients with cognitive decline. Depending upon clinical presentation, the accuracy of clinical history and evaluation alone is variable, and depends upon the expertise of the examiner. Most practitioners can accurately diagnose Alzheimer's disease (AD) on clinical grounds, given its high prevalence and typical symptoms. The accuracy falls rapidly when patients present with early or atypical symptoms, or when patients suffer from other important but less common dementing disorders such as frontotemporal dementia (FTD), prion disease, or vascular dementia (VaD). MRI has utility in the diagnosis and monitoring in many of these disorders, based on the observation of nonspecific but typical findings of atrophy, signal abnormality or progression that match neuropathological patterns of disease involvement.

Diagnostic criteria have been developed for individual illnesses in the research setting, driven largely by the need to appropriately select patients for clinical trials and basic science research. In addition to the results of neurologic examination and other laboratory tests, most of these criteria include specific MRI findings that help to establish a provisional clinical diagnosis. Examples include hippocampal atrophy in AD, burden of white matter disease and territorial infarctions in VaD and reduced diffusion within gray matter in Creutzfeldt-Jakob disease. In most cases these imaging findings are not 100% diagnostic of one particular disorder; rather, they supplement clinical and laboratory data to the point that the ensemble of available data enables distinguishing among different conditions.

Several factors must be taken into account to enable MRI to serve as an adjunct to clinical diagnosis in dementia. First, the examination itself must be of consistent quality and reproducible. In this work, this aim is achieved first through careful development of standardized acquisition protocols with imaging planes and contrasts that consistently depict dementia-specific imaging findings. In addition to being design for accurate subjective review by the trained radiologist, the standardized acquisition developed in this work permits automated, quantitative analysis of brain anatomy to increase diagnostic accuracy. Second, it is critical that imaging observations important for the diagnosis of specific dementia syndromes be routinely reported. For example, the likelihood of VaD depends on the burden of microvascular white matter disease and the location of large-territory arterial infarctions. Third, the relevant imaging observations must be established with high inter-rater reliability. There is substantial variation in the description of cortical atrophy among radiologists. This variability can be reduced through the adoption of standardized rating scales. Finally, radiologists interpreting studies in this domain must be familiar with findings that are may be subtle (such as limbic encephalitis) or uncommon (such as prion disease).

In this guide for standardized acquisition and reporting for MRI in patients with cognitive complaints, the elements of a standardized template for imaging findings are enumerated along 8 individual domains. The role for each reporting within each of these domains is examined in an effort to show how these data elements might assist in diagnosis when imaging is incorporated into a standardized diagnostic pathway. In the discussion that follows, a number of imaging examples are also provided for illustration.

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[1] Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology. Neurology 2001;56:1143–53.

B. SUMMARY OF STRUCTURED REPORTING FOR UCSF-QUEST DEMENTIA PROTOCOL

The elements included in the standardized reporting template for brain imaging in patients with cognitive complaints are as follows:

1. Study quality
2. Qualitative brain volume evaluation
3.   Assessment of limbic structures
4. Characterization of white matter disease
5. Magnetic susceptibility and diffusion
6. Chronic brain injuries
7. Report narrative
8. Recommendation for further brain imaging

Completion of the full structured report according to this design should provide a report that is not only relevant to the diagnosis of dementia, but also can be used as the formal study report and mined for data in the application of diagnostic algorithms.

1. STUDY QUALITY

To assign a level of certainty associated with different imaging findings and ensure sufficient quality of automated volumetric analyses of acquired images, the overall diagnostic quality of each of the acquired MRI sequences should be evaluated.

1A. Volumetric T1 Image Quality

The quality of the volumetric T1 sequence, which is used for quantitative computerized volumetry, is assessed separately according to the following scale:

VOLUMETRIC T1 IMAGE QUALITY ASSESSMENT	
High	No discernable motion and excellent image quality, including gray-white separation.
Satisfactory	No or mild detectable motion artifact but adequate image quality.
Inadequate	Prominent artifacts for which automated volumetric analysis is likely to be inaccurate.

This metric is used to validate the accuracy of the results derived using automated analysis.

1B. Quality of Other Sequences

The imaging sequences included in the UCSF-QUEST dementia protocol, other than volumetric T1, are enumerated in this section. The interpreting radiologist should indicate sequences that were not acquired, or that suffer from motion or other artifacts that is sufficient to render them diagnostically inaccurate. Note that sequences with artifacts may still be considered diagnostically sufficient even if not optimal; the assignment of inadequate quality for any sequence be made when image quality is insufficient to complete the elements from the report below (atrophy patterns, overall burden of white matter disease, etc).

1. STUDY QUALITY

Volumetric T1 Image Quality * must provide value	◯ High - No motion, excellent gray-white contrast ◯ Satisfactory - Motion or contrast degraded but adequate ◯ Inadequate - Artifacts render images inadequate for automated analysis reset
Quality of Other Sequences * must provide value	◯ High - Excellent technical quality, no artifact ◯ Satisfactory - Limited but adequate for interpretation ◯ Inadequate - Artifacts render images insufficient for diagnostic review reset

2. QUALITATIVE BRAIN VOLUME EVALUATION

The elements of the structured template to be evaluated by the radiologist are shown below.

2. QUALITATIVE BRAIN VOLUME EVALUATION

Global Atrophy * must provide value	◯ None - Normal sulcal and gyral thickness ◯ Mild - Opening of cortical sulci with normal gyral thickness ◯ Moderate - Opening of cortical sulci with accompanying gyral atrophy ◯ Severe - Sulci larger than gyri, with "knife blade" gyral narrowing reset
Regional atrophy	☐ Left frontal ☐ Left parietal ☐ Left temporal ☐ Left occipital ☐ Left cerebellar ☐ Brainstem ☐ Right frontal ☐ Rightparietal ☐ Right temporal ☐ Right occipital ☐ Right cerebellar
Ventriculomegaly	◯ No ◯ Yes - central volume loss ◯ Yes - obstructive hydrocephalus ◯ Yes - communicating hydrocephalus (NPH) reset

Atrophy of any tissue results in decreased cellular volume. In brain tissue, atrophy describes a loss of volume within neurons, extracellular space, or glia. Visible loss of brain volume is common in patients with neurodegenerative disorders, and may be generalized or regionally localized. Although automated analysis may be more sensitive to subtle changes in volume and adjust for age, visual analysis remains important as technical artifacts and underlying brain lesions related to prior trauma, infection, hemorrhage, infarction or surgery might sometimes render these algorithms inaccurate. Furthermore, the human eye is quite accurate in determining whether there is disproportionate atrophy involving a specific brain structure.

The evaluation of brain volume is divided global and regional components. Whereas global assessment of volume is based on a general assessment of the prominence of the ventricles, gyri and sulci throughout the brain, regional evaluation requires the subjective determination that atrophy disproportionately involves a certain lobe or type of parenchymal tissue. Global volume loss is nonspecific and can be seen in non-neurodegenerative brain disorders with cognitive symptoms, such as dehydration, endogenous or exogenous steroids, and hypernatremia. It is also a normal feature of aging, as the normal brain loses 0.2% of its volume every year after middle age. When a patient exhibits symptoms of a neurodegenerative illness, however, global atrophy may indicate the presence of widespread neurodegeneration. As examples, diffuse parenchymal atrophy is characteristic of late-stage AD and of secondary chronic multiple sclerosis.

Specificity for neurodegeneration increases when atrophy disproportionately affects individual brain regions, such as the mesial temporal lobes in AD, the frontal and/or temporal lobes in frontotemporal lobar degeneration, or the parietal and occipital lobes in posterior cortical atrophy (Benson's syndrome). Certain neurodegenerative syndromes may also involve structures in the posterior fossa, such as progressive supranuclear palsy or spinocerebellar ataxia. These disorders are often associated with movement disorders clinically.

The global cortical atrophy (GCA) scale, also known as the Pasquier scale, is used to characterize both global and cortical atrophy:

GCA SCALE FOR THE EVALUATION OF ATROPHY		
Score	Assessment	Description
0	None	Normal sulcal pattern and gyral thickness
1	Mild	Opening of the sulci with preservation of gyral thickness
2	Moderate	Opening of sulci with accompanying volume loss of gyri
3	Severe	Severe "knife blade" atrophy with sulci enlarged greater than gyral thickness

In its original description, the GCA scale was designed as a composite score based on assessment of 13 different brain regions.[2] This implementation of the GCA assessment is clearly not practical for everyday clinical use. Instead, the reviewer is prompted to assign a score 0-3 for sulcal vs. gyral thickness in review of overall brain volume.

The observation of regional atrophy should be recorded by lobar involvement. This checklist is designed to characterize the degree of lobar volume loss *beyond the global assessment of parenchymal volume*. When there is symmetric atrophy of the entire supratentorial brain, this section of the report should not be used to indicate the presence of specific lobar atrophy. Instead, this section of the report should be used to indicate the presence only of specific lobar atrophy. Regional atrophy reflects selective neuronal cell death and may be a strong indicator of a specific neurodegenerative disorder (see **Figure 1** for examples). Importantly, hippocampal atrophy is considered separately in evaluation of the limbic system.

[2] Pasquier F, Leys D, Weerts JG et-al. Inter- and intraobserver reproducibility of cerebral atrophy assessment on MRI scans with hemispheric infarcts. Eur. Neurol. 1997;36 (5): 268-72.
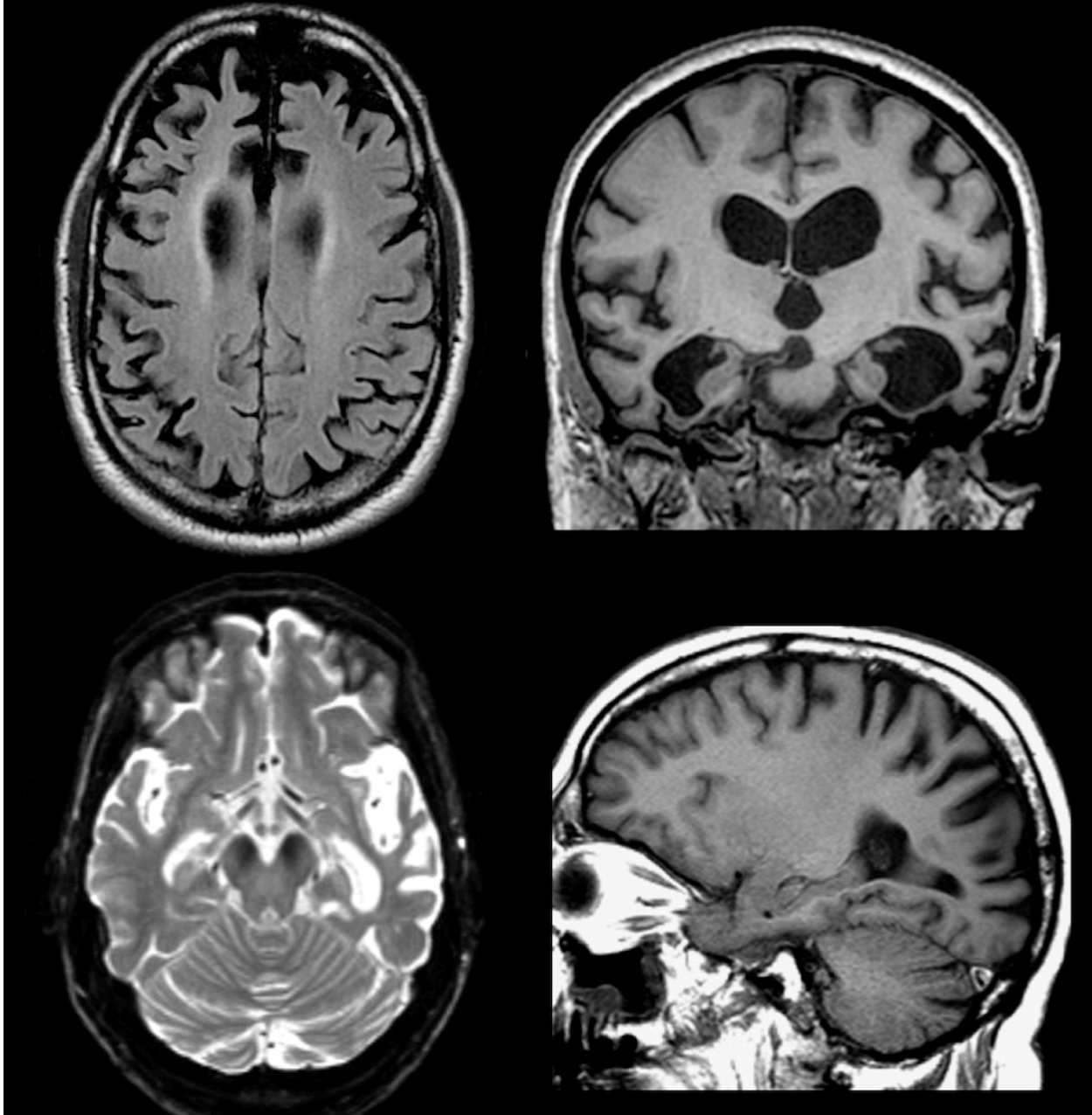
Figure 1. Patterns of regional atrophy due to neurodegenerative disorders. Bifrontal atrophy in behavioral variant frontotemporal dementia (bvFTD, top left), inferior temporal atrophy in semantic dementia with characteristic gaping temporal horns (top right), left perisylvian atrophy in progressive nonfluent aphasia (PNFA, bottom left), and parieto-occipital atrophy in a patient with posterior cortical atrophy (bottom right).

A visual assessment of ventricular size should also be suggested in the qualitative assessment of brain volume. Specifically, when the ventricles are enlarged out of proportion to the supratentorial sulci, the reviewer is directed to indicate that ventriculomegaly is present. Ventriculomegaly is a nonspecific variable that may reflect the presence of central volume loss, related to atrophy of the white matter or deep gray matter structures surrounding the ventricles, or hydrocephalus, which reflects excessive accumulation of CSF within the ventricular system. Stated differently, ventriculomegaly is a feature of

both neurodegenerative disorders (such as progressive supranuclear palsy and AD), and of obstructive or communicating hydrocephalus.

When accompanied by relatively symmetric enlargement of the Sylvian fissures, narrowing of the CSF spaces around the superior sagittal sinus, gaping sulci and bulging within the lateral ventricular walls on sagittal images, suspicion for communicating hydrocephalus (specifically normal pressure hydrocephalus - NPH) should be indicated in the report. These four subjective features (**see Figure 2**) are not diagnostic of this entity, but may support the diagnosis when a patient also suffers from gait abnormalities and/or urinary incontinence. These features are a subset of several imaging findings that have been described as suggestive of this disorder. None of these have high predictive value for NPH or been accepted for use in routine clinical practice. For practical use, we require that at least 2 of 4 of these features be present before this diagnosis is considered.
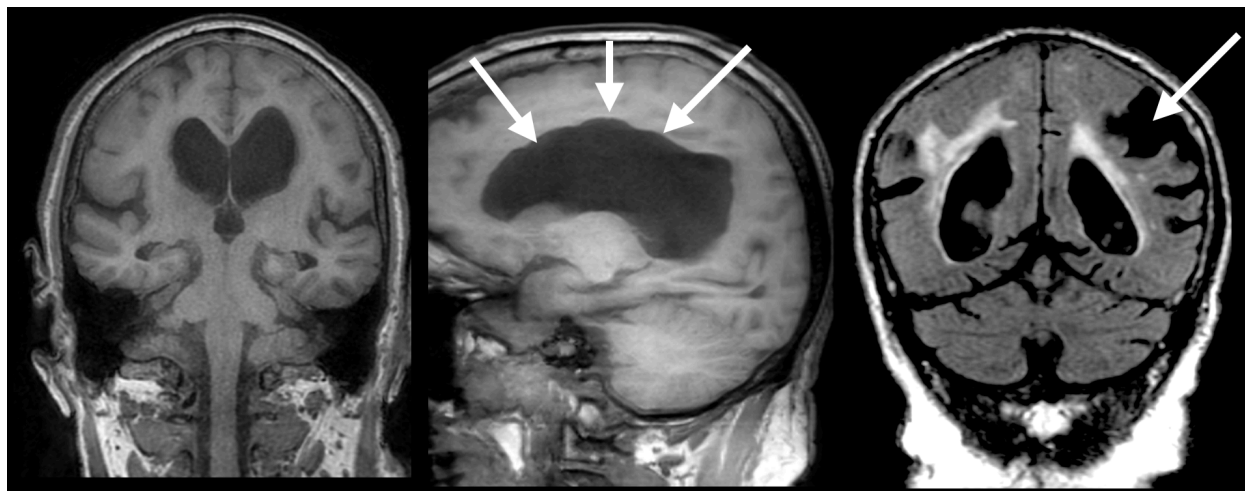
Figure 2. Findings suggestive of "normal pressure hydrocephalus." Typical findings of NPH, including narrowing of sulci near the vertex around the sagittal sinus (left), focal bulging in the margins of the lateral ventricles (arrows, center), and isolated enlarged, "gaping" sulci (arrow, right).

3. ASSSEMENT OF LIMBIC STRUCTURES

The important role that the limbic system plays in cognition, particularly in the encoding and consolidation of working memory, make these structures a common site for both neurodegenerative and non-neurodegenerative disorders that present with symptoms of dementia. The hippocampus and the insula are key structures for this evaluation. Alzheimer's disease, autoimmune limbic encephalitis, and seizure disorders among other diseases may result in atrophy and/or signal abnormality in these areas of the brain. The subjective evaluation of the limbic system is comprised of two separate assessments, one for hippocampal atrophy and the other for limbic signal abnormality.

For hippocampal atrophy, this reporting system employs the 5-point mesial temporal atrophy (MTA) score.[3] This method relies upon review of three structure at the level of the anterior pons,

1. Width of the choroidal fissure
2. Width of the temporal horn of the lateral ventricle

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[3] 2. Duara R, Loewenstein DA, Potter E et-al. Medial temporal lobe atrophy on MRI scans and the diagnosis of Alzheimer disease. Neurology. 2008;71 (24): 1986-92.

3. Height of the hippocampus.

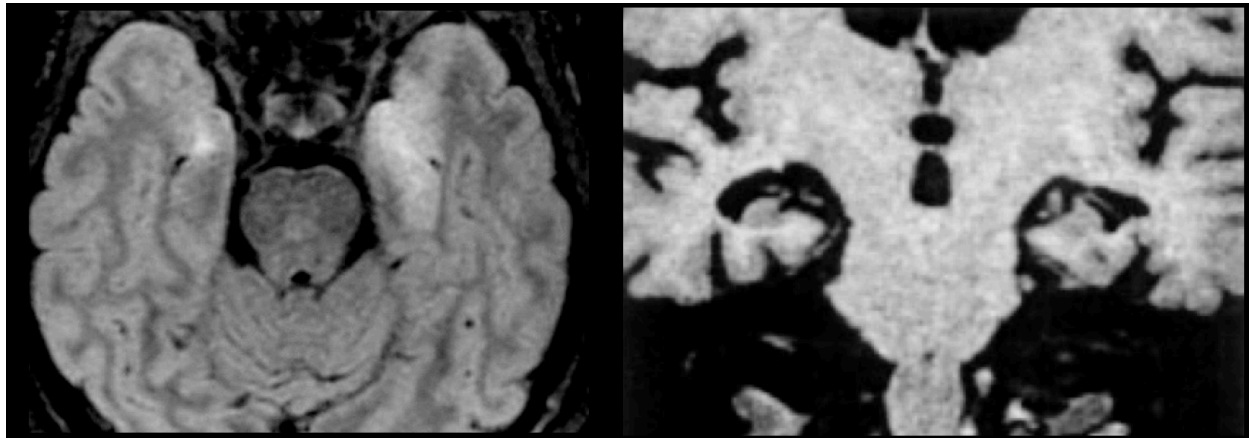to assign a numerical score according to the following system

MTA Score	
Score	Findings
0	No CSF identified around the hippocampal body
1	Mild widening of the choroidal fissure
2	Moderate widening of the choroidal fissure, with mild loss of hippocampal height and mild enlargement of the temporal horn.
3	Marked widening of the choroidal fissure with moderate loss of hippocampal height and moderate enlargement of the temporal horn.
4	Marked widening of the choroidal fissure with severe hippocampal atrophy and enlargement of the temporal horn.

To indicate the observation of hippocampal and/or insular T2, FLAIR, and/or diffusion signal abnormality, the structured reporting template includes a variable for which the presence of abnormal signal can be annotated.

Examples of limbic assessments shown below in Figure 3.

Figure 3. Limbic system abormalities. Left image shows asymmetric T2 hyperintensity involving the medial temporal lobes in a patient with paraneoplastic limbic encephalitis. On the right, a coronal image through the anterior pons in a patient with Alzheimer's dementia shows severe hippocampal atrophy (MTA score 4).

4. CHARACTERIZATION OF WHITE MATTER DISEASE

White matter disease is common, especially in the elderly. Although there are a limited number of MRI appearances of white matter abnormalities, there is a broad range of underlying diseases that may give rise to similar MRI findings, including common senescent microvascular ischemic disease, late-stage multiple sclerosis, hydrocephalus with transependymal flow of CSF, genetic errors in myelination and metabolism, and toxic exposures to name only a few. Characteristic features that help to distinguish among different causes for white matter disease include the extent and location of signal abnormalities, the presence of mass effect or cavitation within involved areas.

The deep white matter component of the Fazekas scale[4] is employed to quantify the extent of abnormal white matter signal in the supratentorial brain. According to this scale, T2 or FLAIR signal abnormality in the deep white matter is quantified on a scale of 0 to 3 (see Figure 4):

Fazekas	
Score	Description
0	Few nonspecific foci of punctate signal abnormality*
1	Scattered punctate foci of signal abnormality
2	Scattered and partially confluent areas of signal abnormality
3	Large confluent areas of signal abnormalty

*Note Fazekas described a score of 0 as absence of any signal abnormality. As mild senescent disease is common with aging, this score is modified to include the presence of a few scattered foci of white matter signal abnormality.

Although the score was originally described for the characterization of senescent microvascular ischemic changes in the white matter, a score of 3 should also be used for confluent areas of signal abnormality that do not have a typical appearance for small vessel ischemic disease, such as may occur in demyelinating or dysmyelinating disorders, toxic or metabolic leukoencephalopathy, or vasculitis. The scale is thus used primarily to characterize the extent (rather than the etiology) of abnormal signal in the deep white matter.

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[4] Fazekas F, Chawluk JB, Alavi A et-al. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol. 1987;149 (2): 351-6.
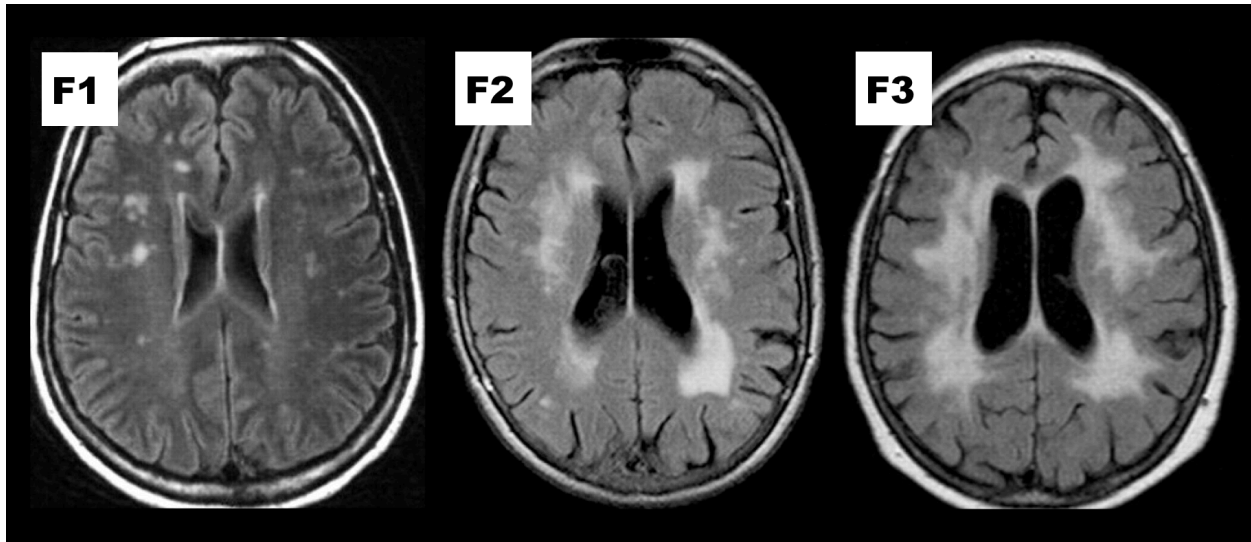
Figure 4. Fazekas scoring for deep white matter disease. Fazekas 1 corresponds to scattered punctate foci of white matter signal (left), which become bridging in the early confluent phase (Fazekas 2, middle), and later diffusely confluent in Fazekas 3 disease (right image).

Additional features of white matter disease that may help in differential diagnosis are indicated separately. Specifically, the involvement of the brainstem and/or cerebellum (infratentorial brain) should be noted, as should extension of the signal to involve the juxtacortical white matter. The presence of mass effect (as may be seen in gliomatosis cerebri or cerebral amyloid angiopathy) and cavitation/vacuolization (more typical of primary demyelinating disease or uncommon disorders such as CADASIL, HDLS, or other adult onset leukodystrophies) should also be noted in this section.

5. MAGNETIC SUSCEPTIBLITY AND DIFFUSION

These two contrasts afforded by MRI can contribute significantly to diagnosis in dementia. Magnetic susceptibility on T2* or susceptibility-sensitive sequences implies the presence of iron deposition, mineralization, or remote blood products. In contrast, diffusion signal reflects the rate of molecular motion of water and thereby provides an indirect measurement of tissue integrity.

| **5. SUSCEPTIBILITY AND DIFFUSION**	
Siderosis	○ No siderosis ○ Localized pial siderosis ○ Diffuse pial siderosis reset
Cerebral microbleeds (CMBs) * must provide value	○ None ○ Few deep ○ Few juxtacortical ○ Multiple, predominantly deep ○ Multiple, predominantly subcortical ○ Multiple, both deep and subcortical reset
Diffusion suspicious for prion disease	○ Yes ○ No reset

5A. Magnetic Susceptibility

Two forms of abnormal susceptibility are captured in the structured report, siderosis and cerebral microbleeds (CMB). Both are common in cerebral amyloid angiopathy, which renders microvessels fragile and prone to hemorrhage. Microbleeds are more common with hypertensive disease, where CMBs tend to arise within the central brain. With siderosis, hemorrhage occurs into the subarachoid space, resulting in hemosiderin staining of the pial surface of the brain.

 The radiologist should indicate the presence of any siderosis and microbleeds using the indicated checkbox. In the case of CMBs, the approximate number and structures involved (gray-white boundaries and/or deep structures) should also be designated.

5B. Diffusion

Diffusion signal is critical to the assessment of prion, or so-called Creutzfeldt-Jakob disease, and is now included in both the UCSF and European diagnostic criteria for these disorders. Reduced diffusion in prion disease is confined largely to the cortical and subcortical gray matter. Most cases (65%) involve both the cortical and subcortical gray matter, with fewer sparing the deep gray matter (33%) or rarely involving only the deep gray matter (Figure 6). Not infrequently, the presence of reduced diffusion is ascribed incorrectly to ischemic injury in these disorders, prompting extensive vascular evaluation. This is especially the case when there is isolated disease of the posterior brain, the Heidenhain variant of prion disease that presents early with visual disturbances. For the confirmation of MRI findings suspicious for prion disease, it is important that reduced diffusion on the diffusion average image ("trace image") be confirmed as reduced diffusion on images of apparent diffusion coefficient (ADC).
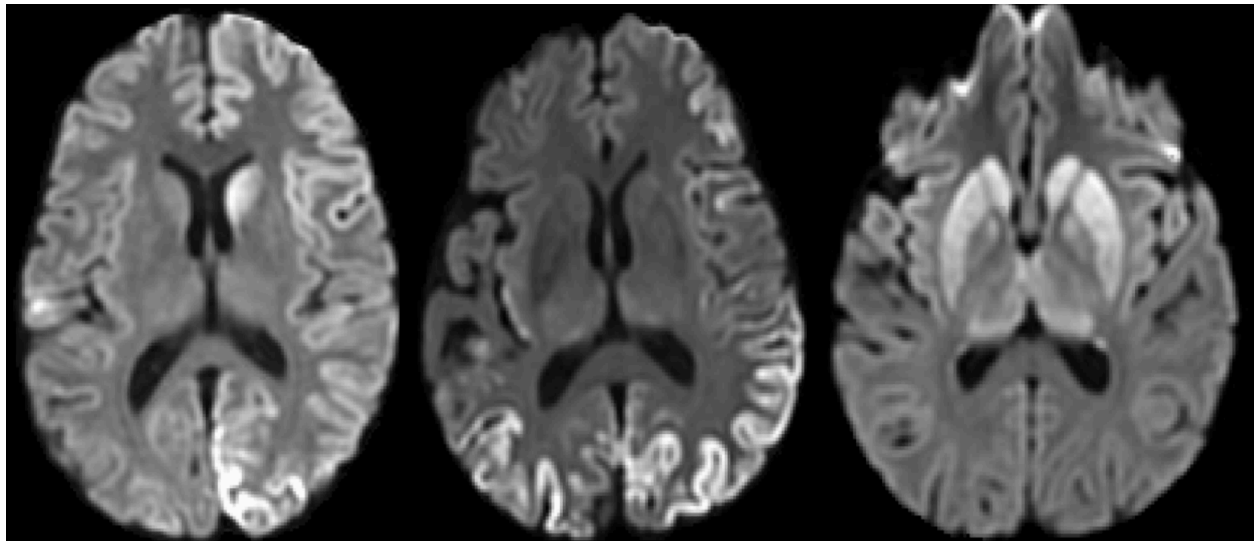
Figure 5. Patterns of reduced diffusion in prion disease. Creutzfeldt-Jakob disease most commonly involves both the cortical and deep gray matter (left), but in approximately 1/3 of cases, the reduced diffusion is confined to the cortical gray matter (middle image). Rarely, reduced diffusion may be seen only involving the deep gray nuclei. In order to confirm the presence of true reduced diffusion, correlation should be made with ADC maps.

6. CHRONIC BRAIN INJURIES

This category is included to designate the location of encephalomalacia related to prior trauma, infection or infarction that may represent a contributor to cognitive decline.

Common sites of traumatic injury in the orbitofrontal, temporopolar and lateral temporal areas of the brain are specifically included. *It is important to distinguish encephalomalacia from atrophy, the former resulting from a remote insult to the brain and the latter suggesting an ongoing process of neurodegeneration.* Encephalomalacia in a vascular territory suggests infarction rather than traumatic injury. There are a number of strategic infarcts that are included in the NINDS-AIRENS diagnostic criteria for vascular dementia (see Figure XX); these are included in this section of the reader template.

Strategic Infarctions
Thalamus, especially bilateral paramedian or multiple lacunar infarctions bilaterally
Angular MCA branch in the dominant (usually left) hemisphere
Dominant hemisphere watershed infarction
Dominant medial temporal lobe
Bilateral anterior cerebral artery
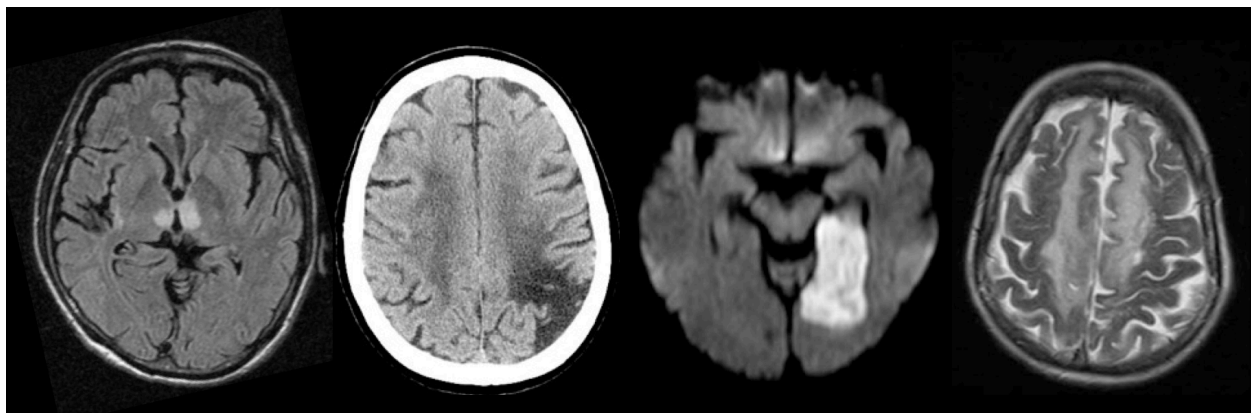
Figure 6. Strategic infarctions in patients with vascular dementia. From left to right, images show bilateral medial thalamic (artery of Percheron infarction), dominant left angular branch MCA, dominant medial temporal, and bilateral ACA infarctions.

7. REPORT NARRATIVE

This section of the template is included for the radiologist to include a standard report narrative, specifically mentioning structural lesions that may contribute to cognitive symptoms and other incidental findings. This section of the report follows the current reporting standard, in which the interpreter is advised to discuss all relevant abnormalities seen on imaging, whether or not they may be associated with a dementing illness.

7. REPORT NARRATIVE

Narrative
* must provide value

Expand

8. RECOMMENDATION FOR FURTHER BRAIN IMAGING

In this final section of the report, several options to ensure further imaging evaluation is obtained when necessary. Specifically, there are options to recommend repeat imaging using a specialized protocol developed separately for rapidly progressive dementia when findings of prion or autoimmune disease, for example, are equivocal for technical reasons on the initial screening MRI evaluation. There is also an option to recommend further imaging with additional sequences such as MRA or gadolinium-enhanced MRI when these may help to characterize a lesion. Finally the option is included for the radiologist to recommend that the study be escalated for review by a subspecialty neuroradiologist with specific expertise in dementia.

8. RECOMMENDATIONS

Further imaging recommended	○ Yes
	○ No
	reset
Expert review requested	○ Yes
	○ No
	reset