Radiology

REVIEWS AND COMMENTARY • REVIEW

Neuroimaging in Dementia: More than Typical Alzheimer Disease

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Conflicts of interest are listed at the end of this article.

See also the review "Functional MRI in Neuro-Oncology: State of the Art and Future Directions" by Pasquini et al in this issue.

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Alzheimer disease (AD) is the most common cause of dementia. The prevailing theory of the underlying pathology assumes amyloid accumulation followed by tau protein aggregation and neurodegeneration. However, the current antiamyloid and antitau treatments show only variable clinical efficacy. Three relevant points are important for the radiologic assessment of dementia. First, besides various dementing disorders (including AD, frontotemporal dementia, and dementia with Lewy bodies), clinical variants and imaging subtypes of AD include both typical and atypical AD. Second, atypical AD has overlapping radiologic and clinical findings with other disorders. Third, the diagnostic process should consider mixed pathologies in neurodegeneration, especially concurrent cerebrovascular disease, which is frequent in older age. Neuronal loss is often present at, or even before, the onset of cognitive decline. Thus, for effective emerging treatments, early diagnosis before the onset of clinical symptoms is essential to slow down or stop subsequent neuronal loss, requiring molecular imaging or plasma biomarkers. Neuroimaging, particularly MRI, provides multiple imaging parameters for neurodegenerative and cerebrovascular disease. With emerging treatments for AD, it is increasingly important to recognize AD variants and other disorders that mimic AD. Describing the individual composition of neurodegenerative and cerebrovascular disease markers while considering overlapping and mixed diseases is necessary to better understand AD and develop efficient individualized therapies.

Supplemental material is available for this article.

The currently available therapeutic options for Alzheimer disease (AD), and neurodegenerative diseases in general, are still limited, except for several treatment options for the motor symptoms of Parkinson disease (PD). Acetylcholinesterase inhibitor treatment may show transient slowing of cognitive decline or even cognitive improvement in AD; however, this beneficial effect is often temporary (1–2 years), then cognitive decline accelerates.

More recently, clinical trials have evaluated therapeutic strategies targeting amyloid deposits (1). Aducanumab is a human monoclonal antibody and the first U.S. Federal Drug Administration–approved disease-modifying drug against AD (2). Leqembi was also approved recently via the accelerated approval pathway. Other similar approaches include gantenerumab (3) or lecanemab (4). The clinical impact of these drugs in clinical trials has been variable and they frequently cause side effects, notably amyloid-related imaging abnormalities (ARIA) that occur in two variants, including brain edema or sulcal effusion (ARIA-E) and hemosiderin deposits (ARIA-H) (5,6). Additional side effects include neuronal disturbance (7), or multiple cerebral hemorrhages related to treatment with a tissue plasminogen activator while receiving antiamyloid treatment (8).

The low success rate of AD treatment trials is due to a combination of factors. The first factor is late diagnosis. Many clinical trials in AD have focused on the late stages of the disease. Already at the onset of cognitive decline, on average, approximately 50% of neurons of the hippocampus are lost, with significant interindividual variability (9). Even if an AD treatment is efficient to slow down or even stop subsequent neuronal loss and cognitive decline, it is very unlikely that treatment will repopulate lost neurons. The second factor is not considering the variants and subtypes of AD. Most clinical trials assume a stereotypical AD disease progression, while several AD variants and subtypes exist. The third factor is viewing AD as an isolated disease while ignoring coexisting diseases, such as cerebrovascular disease. The coexisting diseases may act as a catalyst and accelerate neurodegenerative pathology (10), or both pathologies may interact in their effect on cognitive functioning. The fourth factor is treating AD as having a single cause instead of being a multifactorial disease. The underlying mechanism of AD is still disputed. The prevailing theory suggests misfolded proteins that aggregate (notably amyloid-β and tau), leading to neuronal loss (11). Alternative theories include a neuroinflammation pathway; drugs addressing this theory are fundamentally different from the aforementioned amyloid hypothesis drugs and are still in early phases. Other theories include disease of synapses or mitochondria (12). Even after more than 100 years, to our knowledge, there is no consensus

Abbreviations

AD = Alzheimer disease, CSF = cerebrospinal fluid, DLB = dementia with Lewy bodies, FDG = fluorodeoxyglucose, FTD = frontotemporal dementia, LATE = limbic-predominant age-related TDP-43 encephalopathy, NPH = normal pressure hydrocephalus, PD = Parkinson disease

Summary

The aim of neuroimaging, combined with clinical findings and plasma and cerebrospinal fluid biomarkers, is to help with early diagnosis of neurodegeneration, ideally before the onset of dementia; different subtypes and variants of Alzheimer disease, other dementias, and coexisting diseases are important considerations.

Essentials

- In the age of emerging treatments for Alzheimer disease (AD), early diagnosis is of increasing clinical importance, as is differentiating AD variants from their mimics.
- The diagnostic process should consider mixed pathologies and overlap between neurodegenerative and concurrent cerebrovascular diseases, which are frequent in older age.
- Cerebrovascular diseases share underlying risk factors and have overlapping symptoms with AD; it is vital to consider their contribution to the clinical presentation and the associated treatment options.
- Developments in neuroimaging, including MRI and PET, data-driven disease models, and genetic analyses provide increasing evidence that not all AD is typical AD.
- For emerging treatments to be effective, early diagnosis is essential to prevent neuronal loss, yet subtle early findings make early diagnosis challenging.
- Early diagnosis can probably be achieved only by using a combination of neuroimaging, clinical findings, and plasma and cerebrospinal fluid biomarkers.

regarding the underlying pathology of AD. This suggests that AD is a multifactorial disease with different phenotypes. In concert, these observations imply that dementia is more than typical AD and that AD is not a stereotypical single disease but comes in several variants, subtypes, and with other coexisting diseases. Consequently, neuroimaging, in conjunction with laboratory and genetic testing, should aim for early detection before the onset of dementia.

AD and Its Variants

Mechanism of AD

Most available research on AD assumes a stereotypical disease progressing from cognitively healthy to mild cognitive impairment to AD. While the exact mechanism of AD remains unknown, most studies use the amyloid cascade theory as their basis, represented by the amyloid, tau, and neurodegeneration (ATN) classification system (13). This model assumes initial accumulation of amyloid (A+T–N–), then additional accumulation of tau (A+T+N–), finally leading to neurodegeneration (A+T+N+). This model is also the underlying theory of most current antiamyloid drug developments. When applying this ATN disease progression model to typical memory clinic visitors with subjective or objective cognitive impairment, 53% would follow the model of A+T–N– (16%) to A+T+N– (20%) to A+T+N+ (17%) (14). Among other patterns, such as A–T+N– (6%) or A–T–N+ (9%), 24% would not match this model, thus indicating an alternative disease, such as limbic-predominant age-related TDP-43 encephalopathy (LATE; involving transactive response DNA binding protein 43 kDa [TDP-43] and described herein).

Atypical AD Variants

Besides typical AD, there are several atypical AD variants, determined based on clinical symptoms and neuroanatomic distribution of pathology. Posterior cortical atrophy is a clinical-radiologic variant characterized by posterior atrophy with visuospatial disturbances, found more often in younger patients (15). Behavioral or frontal AD is a variant characterized by symptoms mimicking frontotemporal dementia (FTD) and typically with a more frontal atrophy pattern (16). Individuals with the behavioral variant of AD often have trouble controlling their behavior, clinically overlapping with behavioral variant FTD, which is discussed later in the article. The language variant of AD, for example the logopenic variant of AD, is characterized by difficulties in single-word retrieval, repetition of sentences/phrases, and the presence of phonologic errors (17). This variant clinically overlaps with the logopenic variant of primary progressive aphasia caused by FTD pathology (described herein).

Clinical Use of MRI in Typical or Classic AD

Typical or classic AD is characterized by memory impairment due to predominant atrophy of the hippocampus and surrounding mediotemporal structures (Fig 1A). Atrophy in AD is classified using semiquantitative visual rating scales, such as the mesiotemporal atrophy scale. Alternatively, various image analysis tools exist for automatic volumetry, typically based on volumetric T1-weighted (three-dimensional T1) brain MRI. Normal interindividual variation in hippocampal volume in older controls is in the range of 20%, while the average difference between mild cognitive impairment and healthy controls is around 7%, and AD versus controls is around 12% (18). This indicates that hippocampal volume may discriminate at the group level, yet identification of individual cases of AD is limited, notably at initial stages of the disease. In younger patients, the pattern of atrophy might be predominant in the parietal region with less pronounced atrophy of the hippocampus (Fig 1B). As there is more interindividual variability in the volume of the parietal lobe, it can be more challenging to determine the presence of accentuated parietal atrophy using visual assessments, such as semiquantitative rating scales.

Molecular Imaging in AD via FDG PET, Amyloid PET, and Tau PET

With regards to molecular imaging, fluorodeoxyglucose (FDG) PET is the most established technique in the evaluation of suspected dementia, illustrating brain hypometabolism (19). FDG PET may contribute to the early detection of dementia, as hypometabolism often precedes brain atrophy. Moreover, FDG PET may contribute to the differential diagnosis of dementia, as different patterns of hypometabolism exist (Fig S1). The typical

pattern of hypometabolism in typical AD includes the posterior cingulate cortex and bilateral parietal areas. Due to the metabolic-vascular coupling in the brain, patterns of brain hypoperfusion at arterial spin labeling MRI closely resemble patterns of brain hypometabolism at FDG PET (Fig S2).

While FDG PET measures unspecific brain metabolism, more specific molecular tracers are now available for the diagnosis of AD, especially amyloid PET and tau PET (Fig 2). Amyloid PET may be abnormal up to 10 years before disease onset, yet is not specific for AD dementia, as up to 20%–30% of cognitively healthy older adults exhibit amyloid deposition. Consequently, amyloid PET is notably good to rule out AD. Conversely, tau PET abnormality is more closely related to disease onset and is useful to rule in AD. The combination of tau PET and amyloid PET scans with positive findings in a cognitively unimpaired individual carries a higher risk of future cognitive decline (20).

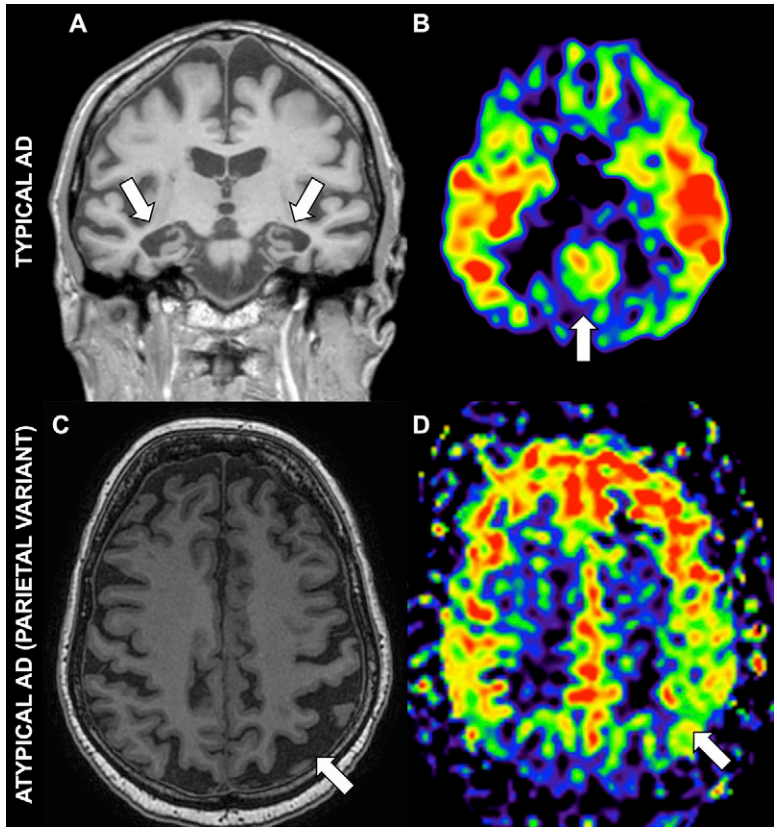

Figure 1: **(A, B)** MRI scans in an 83-year-old male patient with typical Alzheimer disease (AD). Coronal T1-weighted image **(A)** shows predominant atrophy of the hippocampus (arrows). This is associated with hypoperfusion of the posterior cingulate cortex (arrow), known as absent light bulb sign, on the arterial spin labeling image **(B)**. In a healthy individual, the perfusion at rest of the posterior cingulate cortex should be as least as high as the remaining gray matter resulting in a "light bulb" appearance. **(C, D)** MRI scans in a 65-year-old male patient show predominant parietal atrophy (arrows) suggestive of an atypical parietal variant of AD. The parietal variant of AD often affects younger patients and can be asymmetric. Corresponding arterial spin labeling image **(D)** shows associated hypoperfusion, which is likely overestimated by the atrophy/partial volume effect.

Imaging-based Subtypes of AD Based on Patterns of Brain Atrophy

Recently, neuroimaging studies have grouped large data sets with advanced image analysis procedures to define subtypes of AD based on imaging patterns.

A recent study pooled more than 1000 cases of amyloid PET in a data-driven analysis with the intention to disentangle disease subtype and disease stage at the same time (22). This study identified three pattern subtypes, which are frontal, parietal, and occipital (Fig S3A). It might appear contradictory that more recent PET studies suggest subtypes of AD, while previous histopathologic studies suggested a more unique and stereotypical AD pattern. Several factors explain this apparent contradiction. First, large data sets allow for clustering analysis, which is necessary to detect such subtypes. Second, the differences between the subtypes are most pronounced at the initial stages of the disease. At later stages, the subtypes converge and it is no longer possible to disentangle them. It is easier to combine large PET data sets across different centers and include presymptomatic cases than postmortem histopathologic grading. Postmortem grading is usually done in smaller data sets and at later stages of the disease. Third, many previous analyses are not done with the specific intention to discriminate subtypes but rather to describe average abnormality in a group. If the newly observed subtypes are averaged into one single type, the resulting pattern resembles the established disease pattern known from histopathologic studies (Fig S3B). Of note, there is a certain degree of concordance between clinically defined AD variants and imaging-defined AD subtypes, such as frontal dominant AD.

When applying this data-driven stage and type segregation, the findings will be close to that of tau PET, which again results in the segregation of subtypes of tau accumulation (23). These four subtypes are limbic (typical), mesiotemporal lobe sparing, posterior, and left temporal, partially reflecting the aforementioned amnestic, behavioral, visuospatial, and language variants, respectively.

Genetic Subtypes and Genetic Risk Factors for AD

An uncommon form of familial early-onset AD is inherited as an autosomal-dominant gene mutation (the current best-established mutations are amyloid-β precursor protein, presenilin 1, and presenilin 2). In contrast, in the more common typical, late-onset, and sporadic AD, genetic mutations are less established. But several identified genetic variants increase the risk of AD and may lead to familial patterns of AD risk. Today, the most important genetic risk factor for AD is the apolipoprotein E or *APOE* gene. Each person inherits two *APOE* alleles, one from each biologic parent. *APOEE3* is the most common allele and carries a neutral risk. *APOEE4* increases the risk for AD, notably in homozygotes (24,25). In contrast, *APOEE2* is relatively rare and is associated with decreased risk of AD (26). In dominantly inherited AD, amyloid deposition at PET is detected 15 years before the onset of expected symptoms and a decline in amyloid-β peptide (Aβ42) in cerebrospinal fluid (CSF) can be detected even earlier (27).

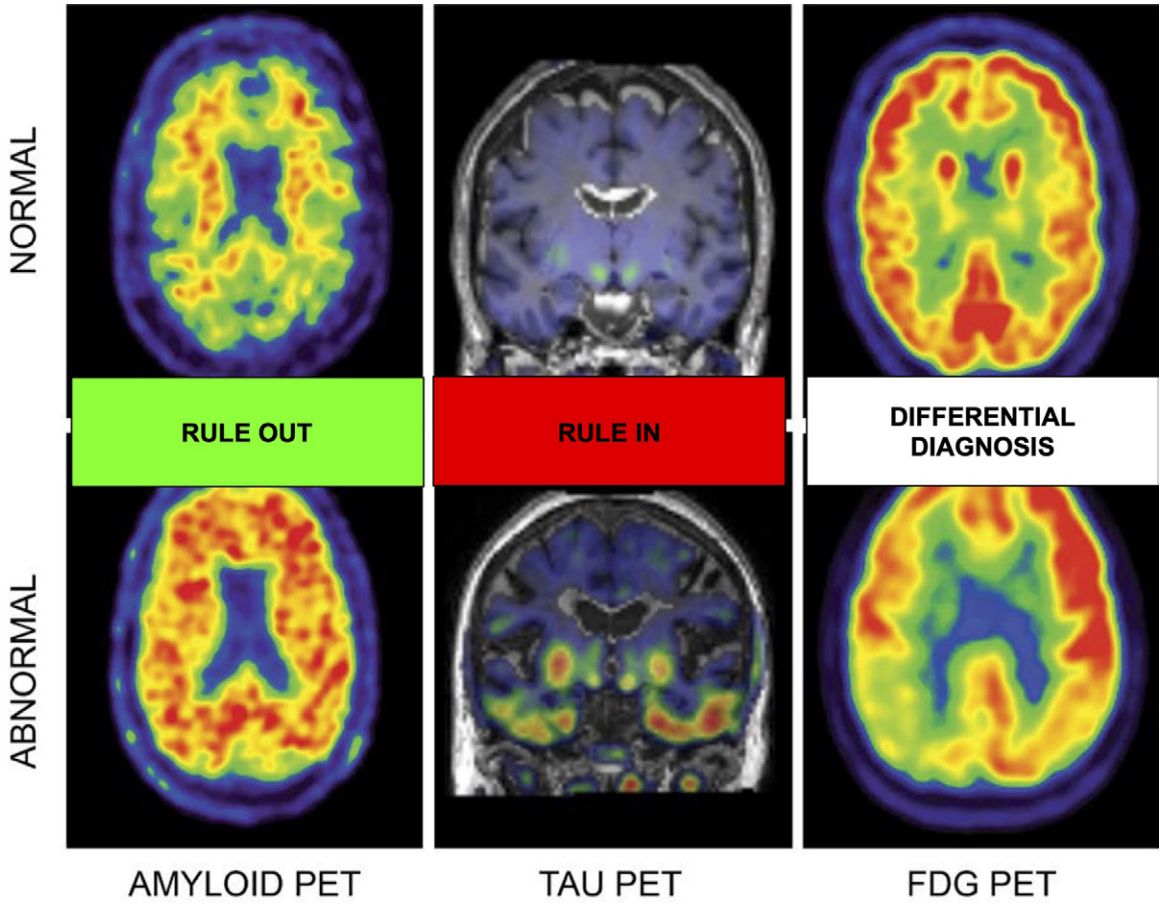

Figure 2: Left: Normal amyloid PET image (top) shows uptake in the white matter, while the abnormal amyloid PET image (bottom) shows additional cortical uptake. Amyloid PET is notably useful to rule out Alzheimer disease (AD). Middle: Tau PET images show normal uptake is very minimal (top), while abnormal tau PET uptake is typically most pronounced in the temporal regions (bottom). Tau PET is notably good to rule in AD. Right: Fluorodeoxyglucose (FDG) PET images show normal homogeneous uptake in superficial and deep gray matter (top), while the typical abnormal FDG PET pattern in AD (bottom) includes hypometabolism in the posterior cingulate cortex and bilateral parietal areas (in this case asymetric and more pronounced in the right hemisphere). Adapted and reprinted, under a CC BY license, from reference 21.

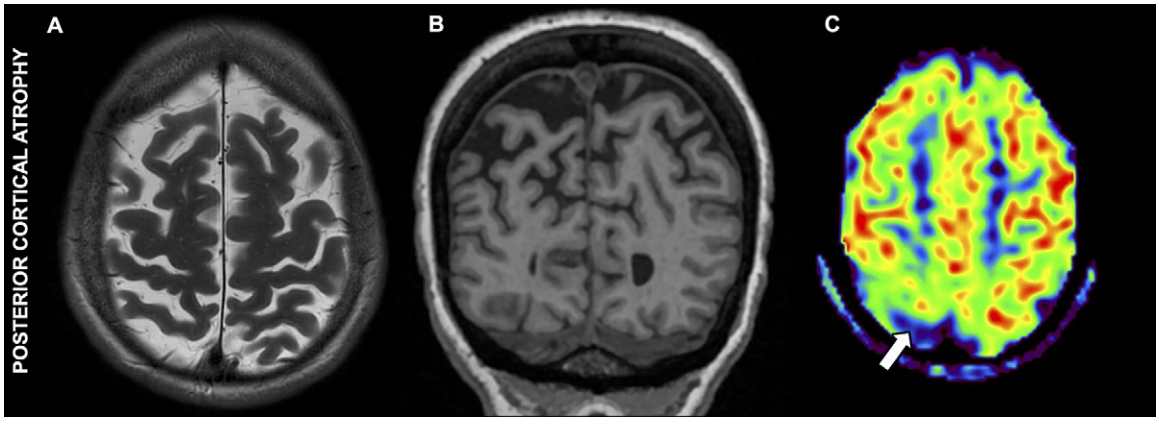

Figure 3: **(A)** Axial T2-weighted and **(B)** coronal T1-weighted MRI scans in a 61-year-old female patient with posterior cortical atrophy and impaired visual-spatial integration show predominant atrophy in the right-dominant parietal area, which is associated with hypoperfusion (arrow) on the **(C)** arterial spin labeling image.

Liquid Biomarkers

Recently, substantial progress has been made in liquid biomarkers based on CSF and blood samples, which will likely change the role of imaging of AD and related diseases in the future. Discussion of those liquid biomarkers is beyond the scope of the current review article, and we refer to a recent review article (28).

Underlying Disease, Atrophy Pattern, or Clinical Manifestation

There are several ways to classify dementia types, including symptom-based, imaging-based, and pathology-based approaches. Different underlying molecular pathologies can lead to similar clinical symptoms and atrophy patterns, which makes the classification of dementia types purely based on symptoms

and imaging appearances problematic. For example, the underlying pathology of posterior cortical atrophy, defined by parietal volume loss and visuospatial symptoms, can be related to AD, dementia with Lewy bodies (DLB), or corticobasal degeneration (29). Another example is patients presenting with primary progressive aphasia who may have AD or FTD as the underlying pathology.

Posterior Cortical Atrophy

Posterior cortical atrophy (PCA) consists of predominant parietal atrophy combined with a typical clinical presentation (15). This is a frequent mode of presentation in younger patients, with visuospatial disturbances and a lesser degree of hippocampal atrophy (Fig 3). Oftentimes, amyloid plaques and neurofibrillary tangles are present, similar to typical AD, yet in a different spatial distribution. Also, *APOEE4* is less often present in patients with PCA compared with patients with typical AD. The differential diagnosis of posterior cortical atrophy includes DLB, with abnormal dopamine transporter imaging of the striatum, and corticobasal degeneration with cerebellar atrophy and asymmetric parietal atrophy.

Primary Progressive Aphasia

Primary progressive aphasia is a neurologic syndrome characterized by slow progressive impaired language capabilities (30). The commonly used classification distinguishes the clinical subtypes of primary progressive aphasia into the semantic variant (also still frequently referred to as semantic dementia), the logopenic variant, and the nonfluent agrammatic variant (Fig 4). It is important to realize that these clinical categories have variable underlying pathology. Whereas AD pathology is frequently associated with the logopenic variant, the semantic and nonfluent agrammatic variants link to frontotemporal lobar degeneration with primary tau or TDP-43 pathology (31).

Other Types of Dementia That Mimic AD

While AD is the most common type of dementia, it is not the only type of dementia. Typical distributions of cases of dementia types in a memory clinic setting (Fig 5) show that

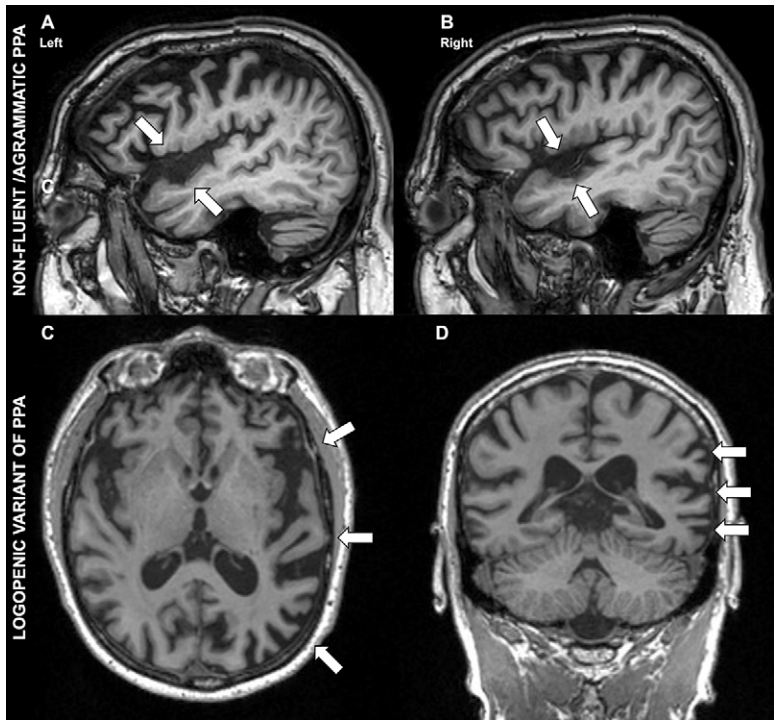

Figure 4: **(A)** Left and **(B)** right sagittal T1-weighted MRI scans show typical atrophy pattern consisting of left-dominant peri-insular atrophy with anterior-to-posterior gradient (arrows) in nonfluent/agrammatic primary progressive aphasia (PPA), which is clinically characterized by word production problems and effortful and nonfluent speech. **(C)** Axial and **(D)** coronal T1-weighted MRI scans show typical atrophy pattern consisting of left-dominant peri-insular atrophy extending posteriorly into the parieto-occipital cortex (arrows). The logopenic variant of primary progressive aphasia is characterized by difficulty finding words and slow speech, but preserved understanding.

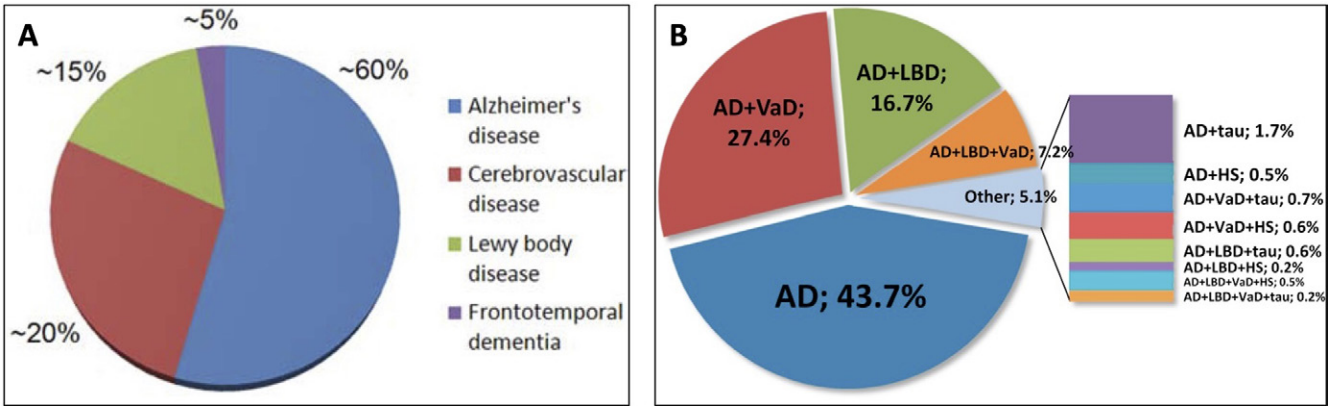

Figure 5: **(A)** Pie chart shows the classic distribution of dementia types in a memory clinic setting, where most cases (60%) are Alzheimer disease (AD). Although AD is attributed to the majority of cases, 40% are not AD. Reprinted, with permission, from reference 32. **(B)** Pie chart shows, according to recent studies, that within the AD group, less than half of cases are isolated AD, while more than half of cases are various combinations of mixed pathologies that include AD. HS = hippocampal sclerosis, LBD = Lewy body dementia, VaD = vascular dementia. Reprinted, under a CC BY license, from reference 33.

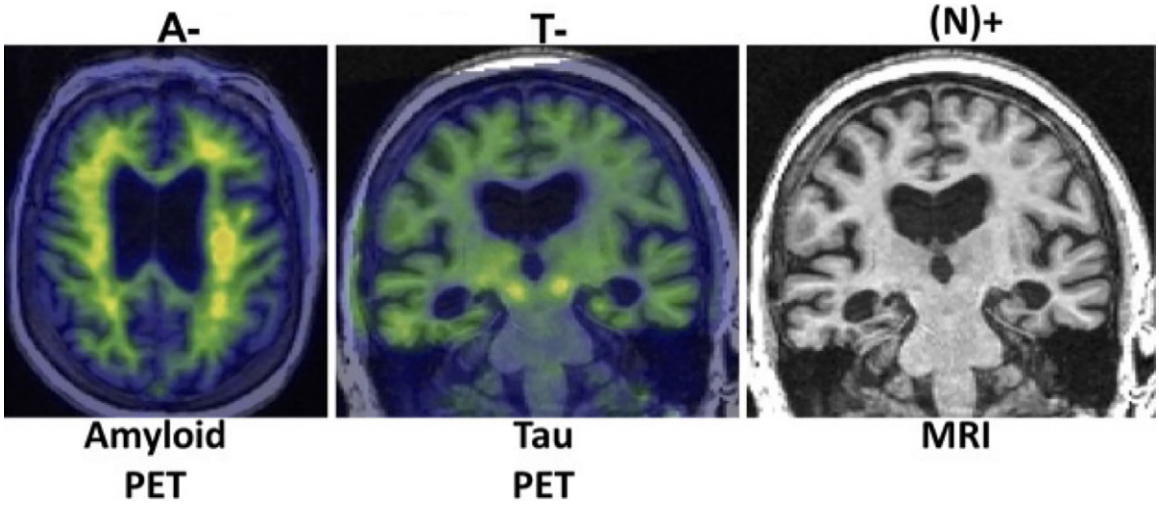

Figure 6: Amyloid PET, tau PET, and MRI scans in an 86-year-old female patient who was diagnosed during life as having a suspected non–Alzheimer disease (AD) pathology show an amyloid, tau, and neurodegeneration (ATN) pattern of A–T–N+, respectively. Autopsy within a year confirmed limbic-predominant age-related TDP-43 encephalopathy (LATE). Note that the predominant hippocampal atrophy mimics AD, and in the absence of amyloid and tau PET imaging, LATE may be indistinguishable from AD. Reprinted, with permission, from reference 34.

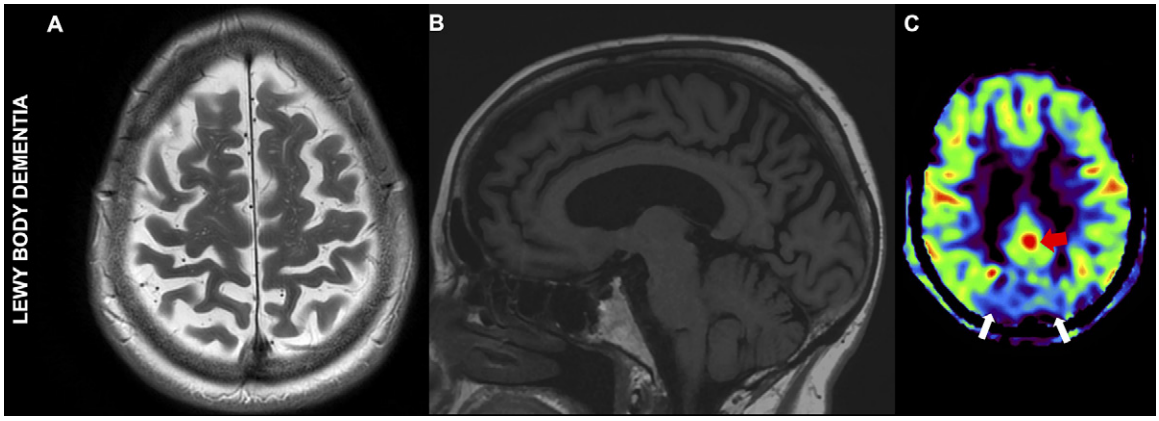

Figure 7: **(A–C)** Axial T2-weighted **(A)** and sagittal T1-weighted **(B)** MRI scans show only minor structural abnormalities, most commonly mild parietal atrophy, as is typical with standard MRI sequences. Fluorodeoxyglucose (FDG) PET or arterial spin labeling **(C)** images typically show preserved metabolism (FDG PET) or perfusion (arterial spin labeling) in the posterior cingulate cortex, known as cingulate island sign, yet reduced metabolism (FDG PET) or perfusion (arterial spin labeling) in the parieto-occipital region (arrows).

approximately 60% of cases are AD, while approximately 15% are DLB and 5% are FTD. Consequently, the ratio of the clinical diagnosis of AD to DLB is 4:1 and AD to FTD is 12:1. A PubMed search (accessed on December 31, 2022) yielded 218 214 entries for AD since 1913, 9727 for DLB since 1961, and 12 656 for FTD since 1948, which corresponds to ratios of AD to DLB of 22:1 and AD to FTD of 17:1 (Fig S4). These are simplified numbers, yet this illustrates the overrepresentation of AD in scientific research with respect to its clinical prevalence.

The following section discusses the differential diagnosis of other forms of dementia that may be in the differential diagnoses for AD, either because of overlap in clinical symptoms or in imaging characteristics.

Of note, hippocampal atrophy is not specific to AD but is a feature of several other forms of dementia. Consequently, focusing on hippocampal volume alone may lead to wrong diagnoses.

Limbic-Predominant Age-related TDP-43 Encephalopathy

LATE neuropathologic change was recently defined as a TDP-43 proteinopathy in older adults, with or without coexisting hippocampal sclerosis pathology (Fig 6) (34). Associated with an amnestic dementia syndrome, this type of dementia may mimic AD clinically and radiologically and distinguishes itself from FTD with TDP-43 pathology as it affects very older adults and has a relatively restricted neuroanatomic distribution of TDP-43 proteinopathy (34). The neuroimaging pattern includes hippocampal atrophy mimicking typical AD but without amyloid deposition at molecular imaging. This dementia is thus a mimic of AD (clinically and radiologically). It is also an example of an entity not following the aforementioned amyloid, tau, and neurodegeneration (ATN) model. Assessment of amyloid status (using CSF or PET) is the only safeguard to differentiate AD from LATE.

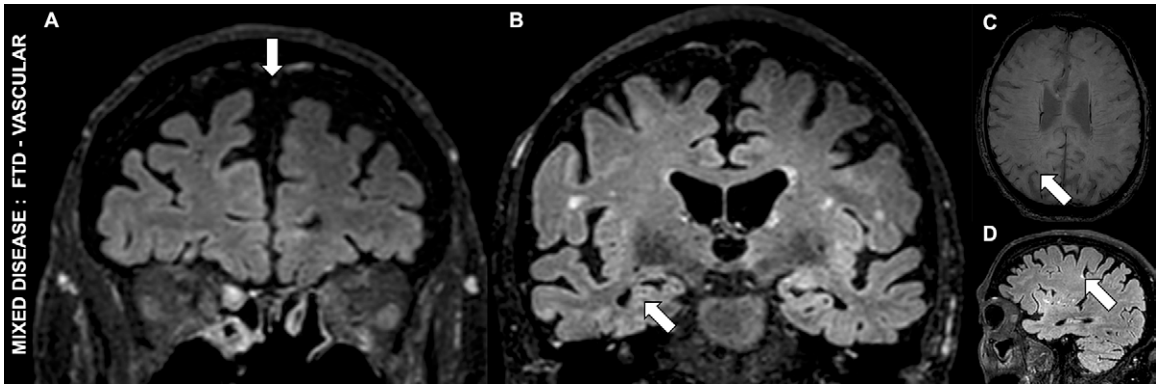

Figure 8: **(A, B)** Coronal T2-weighted fluid-attenuated inversion recovery MRI scans in a 79-year-old male patient with progressive cognitive decline show predominant frontal atrophy (arrow in **A**) and, to a lesser degree, mesiotemporal atrophy (arrow in **B**) with a score of 1, suggestive of behavioral variant frontotemporal dementia (FTD). **(C)** Susceptibility-weighted MRI scan in the same patient shows a few cerebral microbleeds (arrow), while mild white matter pathology (Fazekas grade 1) is also evident. **(D)** T2-weighted fluid-attenuated inversion recovery MRI scan in the same patient shows a cortical microinfarct (arrow), suggesting a cerebrovascular disease component. In total, these findings suggest mixed disease with FTD and cerebrovascular disease.

Dementia with Lewy Bodies

DLB belongs to the family of synucleinopathies, together with PD and multiple system atrophy. Characterized by the accumulation of Lewy bodies, this type of dementia shares pathologic features with PD. Sometimes considered as two ends of a DLB spectrum, PD may transition from initial motor symptoms to later cognitive decline, while DLB may transition from initial cognitive decline to later motor symptoms. In analogy to other forms of dementia discussed herein, the DLB/PD spectrum has clinically variable presentations based on overlapping or underlying pathology (35). In addition to the extrapyramidal findings most pronounced in PD, typical symptoms include rapid eye movement, or REM, sleep disturbances and visual hallucinations found notably in DLB.

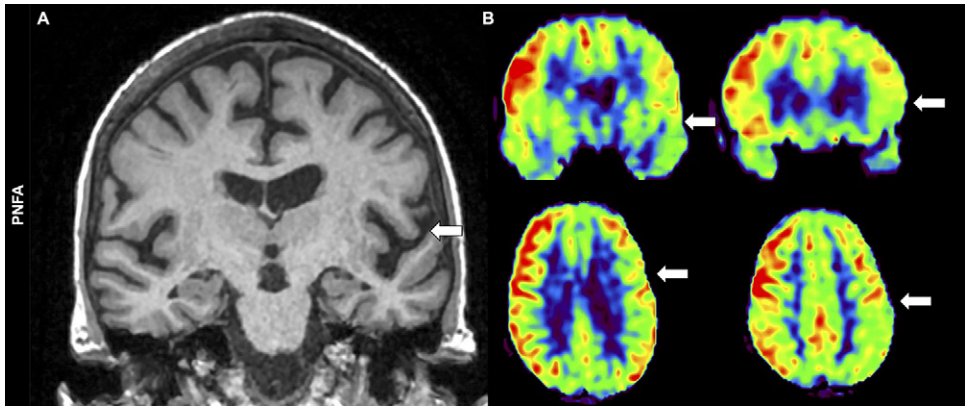

Figure 9: **(A)** Coronal T1-weighted MRI scan in a 76-year-old female patient with early progressive nonfluent aphasia (PNFA) shows mild asymmetric left-dominant atrophy (arrow) in the peri-insular region. **(B)** Arterial spin labeling MRI scans in the same patient show associated slight hypoperfusion (arrows) in the left-dominant peri-insular region and, to a lesser degree, frontoparietal regions.

Of note, DLB spectrum is common, yet typically has a less obvious atrophy pattern on standard structural images (including mild atrophy of parietal regions and hippocampal subregions on structural CT or MRI scans) and is, therefore, easily overlooked from a neuroradiologic perspective. Dopamine imaging is essential for its diagnosis.

Genetic Subtypes and Genetic Risk Factors

Less research has been performed to identify the genetic subtypes and risk factors of DLB compared with AD (36). We know today that DLB shares risk factors with AD, in particular, *APOEE4*. Moreover, as already discussed, DLB overlaps with PD (36).

Structural Subtypes and MRI Markers

Unlike the hippocampal predominant atrophy in typical AD, DLB and PD are not associated with an obvious pattern of brain atrophy. Compared with AD, DLB has milder hippocampal atrophy, occurring only at later stages, that may have different spatial predominance (eg, preserving the cornu ammonis 1 subfield) (37). Sometimes, some mild parietal and occipital atrophy is visible (Fig 7). Consequently, standard structural MRI and CT have a blind spot for the diagnosis of DLB and PD. This might be one of the reasons explaining why DLB remains underrecognized, at least from a radiologic perspective.

Recently, abnormal appearance of nigrosome 1 (a region in the substantia nigra also known as "swallow tail sign") based on susceptibility-weighted imaging was introduced as an MRI marker in PD (38). Abnormal imaging of nigrosome 1 behaves similar to dopamine imaging in nuclear medicine (the most commonly used technique being ^{123}I-ioflupane SPECT). Both MRI of nigrosome 1 and nuclear medicine dopamine imaging are abnormal in PD and DLB, yet normal in AD or FTD. Consequently, abnormal appearance of nigrosome 1 in DLB may resolve the blind spot of MRI for the diagnosis of DLB (Fig S5) (39,40). Imaging of nigrosome 1 is without any doubt a challenge, and requires an experienced reader and critically depends

on appropriate imaging parameters (41). However, it is clinically applicable with minimal additional acquisition time and cost, and without irradiation, assuming that most patients with neurodegenerative disease already undergo MRI. Imaging of nigrosome 1 is probably best applied if the intention is not to replace dopamine imaging, yet to triage patients for subsequent dopamine imaging to improve diagnostic yield (42). Alternative imaging techniques include heavily T1-weighted neuromelanin-sensitive sequences, which are also possible at an individual level and in clinical routine, although might be even more challenging.

Nuclear Medicine

Unlike the unspecific structural CT and MRI findings, nuclear medicine has a vital role in the diagnosis of DLB/PD (43).

Dopamine Imaging

Dopamine imaging is the most established and specific nuclear medicine technique for DLB/PD (44). ^{123}I-ioflupane SPECT, also known as dopamine transporter, or DAT, scan, is the best-known technique, yet other dopamine tracers and techniques do exist. As a simplification, the normal dopamine uptake in the striatum has a bilateral comma-shaped pattern. In DLB and PD, the tracer uptake of the putamen decreases and results in a bilateral dot-like appearance (often asymetric, notably at early stages of the disease). Dopamine imaging results are abnormal in DLB and PD (and atypical parkinsonian syndromes) but normal in AD and FTD.

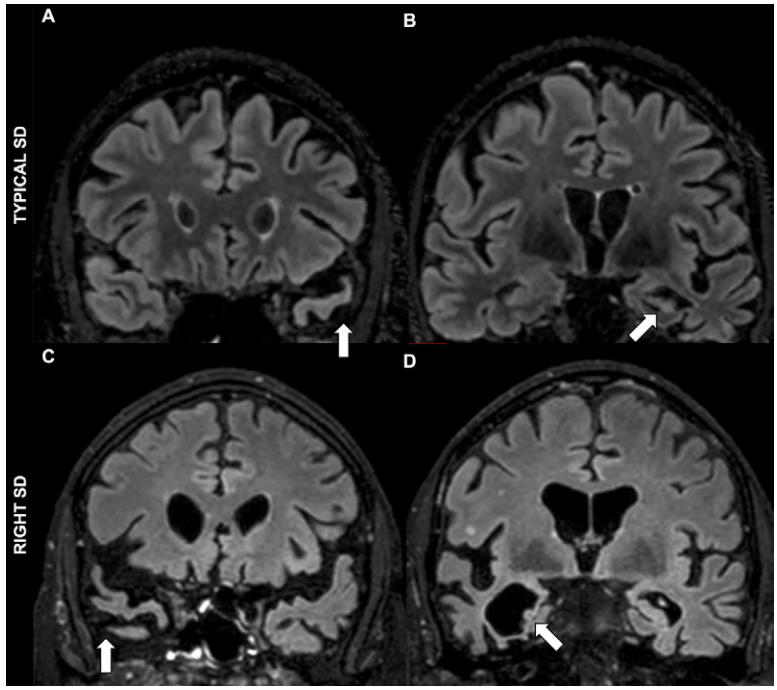

Figure 10: **(A, B)** Coronal T2-weighted fluid-attenuated inversion recovery MRI scans in a 73-year-old female patient with progressive cognitive decline and semantic difficulties show predominant atrophy of the left temporal pole (arrow in **A**), including the asymmetric hippocampal atrophy (arrow in **B**) suggestive of semantic dementia (SD). There is only very minor cerebrovascular disease. **(C, D)** Coronal T2-weighted fluid-attenuated inversion recovery MRI scans in a 63-year-old male patient with progressive cognitive decline and trouble recognizing faces show predominant atrophy of the right temporal pole (arrow in **C**), including the asymmetric right-dominant hippocampal atrophy (arrow in **D**) suggestive of right temporal variant frontotemporal dementia. There is only very minor cerebrovascular disease.

Alternative PET Tracers

Standard FDG PET typically shows a specific pattern of hypometabolism in DLB involving the bilateral parietal and occipital areas while sparing the posterior cingulate (giving rise to the cingulate island sign). In contrast, the typical pattern of FDG PET hypometabolism in AD spares the occipital areas but involves bilateral parietal and occipital areas. Typical FDG hypometabolism in FTD also spares the occipital region and involves frontoparietal areas.

A certain amount of amyloid-β pathology is also found in patients with DLB, and amyloid PET findings may therefore be positive. However, in a study with pathologically proven diagnoses, carbon 11 (^{11}C) Pittsburgh compound B uptake on PET images was lower in DLB than in AD (45).

Frontal Dementia Subtypes

Representing a heterogeneous group of dementia subtypes, FTD is part of the larger entity referred to as frontotemporal lobar degeneration, which also includes other disorders such as progressive supranuclear palsy and corticobasal degeneration, depending on the classification system used (46).

These dementia subtypes have variable underlying pathology, atrophy patterns, and clinical presentations. The latter can be broadly categorized into language-led presentations (primary progressive aphasia) and behavior-led presentations (disintegration of personality, sometimes misdiagnosed as psychiatric disorders) (31,47). Usually presenting at a younger age than AD, FTD is more frequently associated with gene mutations, especially in familial cases. In addition, they can be associated with other neurologic conditions, such as parkinsonism or motor neuron disease. A detailed discussion of frontotemporal lobar degeneration goes beyond the scope of this review; therefore, the focus is on the most common subtypes relevant in the current context and those that may mimic AD, including behavioral variant FTD, progressive nonfluent aphasia, and semantic dementia.

Of note, hippocampal atrophy, often asymmetric, is a typical feature of frontotemporal lobar degeneration. This might be diagnosed as AD when focusing only on hippocampal atrophy; however, as it is also a feature of FTD, associated frontal atrophy should be investigated.

Clinical Use of MRI for Differentiation of FTD Subtypes

Behavioral variant FTD.—Behavioral variant FTD is the most common subtype of FTD and is characterized by predominant fronto-temporo-parietal atrophy, typically with an

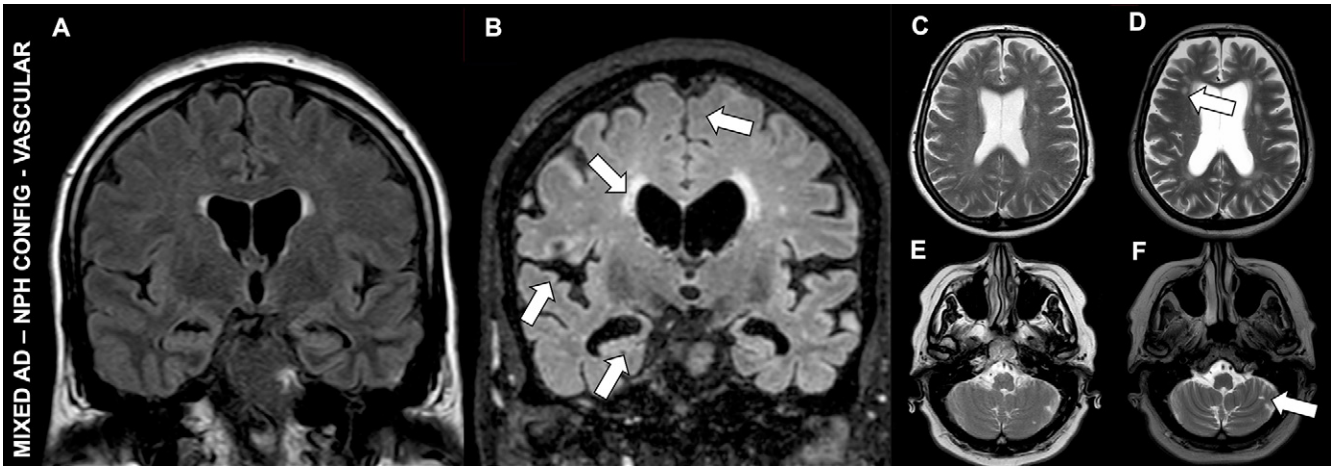

Figure 11: **(A–F)** MRI scans in a 73-year-old female patient with progressive cognitive decline include a coronal T2-weighted fluid-attenuated inversion recovery MRI scan **(B)** that shows progressive hippocampal atrophy with respect to imaging 14 years prior **(A)**, suggesting Alzheimer disease (AD) neurodegeneration. There is additional appearance of normal pressure hydrocephalus (NPH) configuration, including dilated ventricular system, slight transependymal transudation, crowding of sulci at the vertex, V-shaped corpus callosum, and enlargement of sylvian fissure (arrows in **B**). Note that dilation of temporal horns is a feature of NPH configuration and might lead to overestimation of hippocampal atrophy. Moreover, there are progressive signs of vascular disease that include progressive white matter hyperintensities (arrow in **D**) on axial T2-weighted MRI scans **(C, D)** and a new cerebellar microinfarct (arrow in **F**) in proximity to preexisting cerebellar microinfarcts **(E, F)**. In total, these findings suggest mixed disease that includes AD-type neurodegeneration, NPH configuration, and a cerebrovascular component. Note, there are some imaging features of NPH configuration but not the full radiologic signs of NPH or the typical clinical presentation of NPH.

anterior-to-posterior gradient. Mesiotemporal atrophy is often associated, although typically less pronounced compared to AD and more often asymmetric (Fig 8).

Progressive nonfluent aphasia.—Progressive nonfluent aphasia is a form of FTD characterized by word production problems and effortful and nonfluent speech, with language comprehension remaining intact. Imaging shows asymmetric focal atrophy of the inferior frontal gyrus and peri-insular region, most frequently on the left side. (Fig 9). There are, however, wide variations in severity and posterior extension of the atrophy.

Semantic dementia.—A disorder affecting language comprehension (losing the meaning of words and images), semantic dementia is characterized by focal atrophy of the temporal pole and, in particular, the fusiform gyrus, classically on the left side. Asymmetric mesiotemporal atrophy is typical, but as the disease progresses the contralateral side usually also gets involved (Fig 10A, 10B).

Right temporal variant FTD.—Right temporal variant FTD is characterized by mirror-symmetric right-dominant temporal pole atrophy. This type of dementia is clinically much more rarely diagnosed than semantic dementia (Fig 10C, 10D). It remains controversial whether right temporal variant FTD is less common than left-lateralized typical semantic dementia; speculations include that, in most individuals, the left hemisphere is dominant and predominantly involved in language processing and, therefore, might degenerate faster. Alternatively, right temporal variant FTD might be underdiagnosed as affection of the nondominant right hemisphere as it has less evident clinical symptoms.

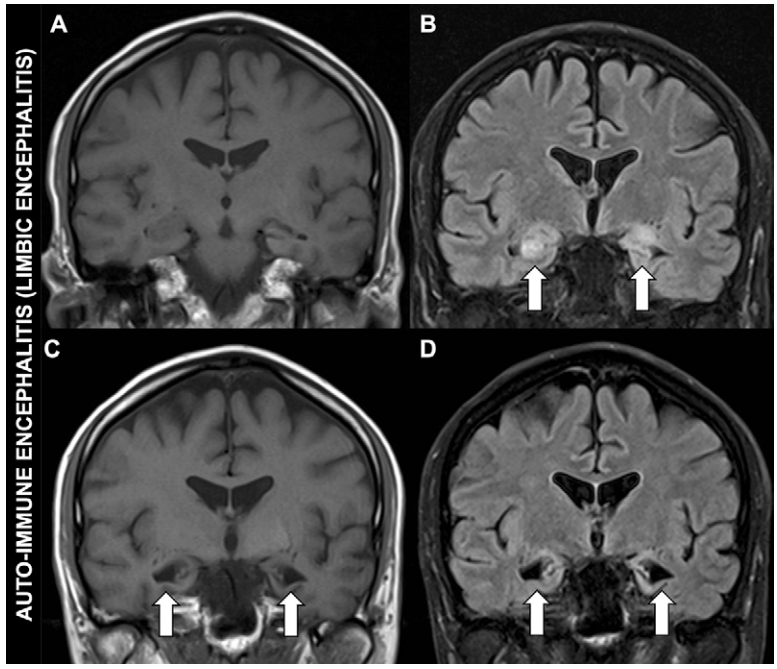

Figure 12: **(A, B)** Coronal T1-weighted **(A)** and coronal T2-weighted fluid-attenuated inversion recovery **(B)** MRI scans in a patient with testicular germinoma show abnormality in the bilateral hippocampi (arrows) suggestive of autoimmune encephalitis (limbic encephalitis). **(C, D)** Coronal T1-weighted **(C)** and coronal T2-weighted fluid-attenuated inversion recovery **(D)** MRI scans in the same patient 1 year later show hippocampal volume loss (arrows) without a vascular component. If only the follow-up imaging had been available, the hippocampal volume loss could have been misinterpreted as Alzheimer disease.

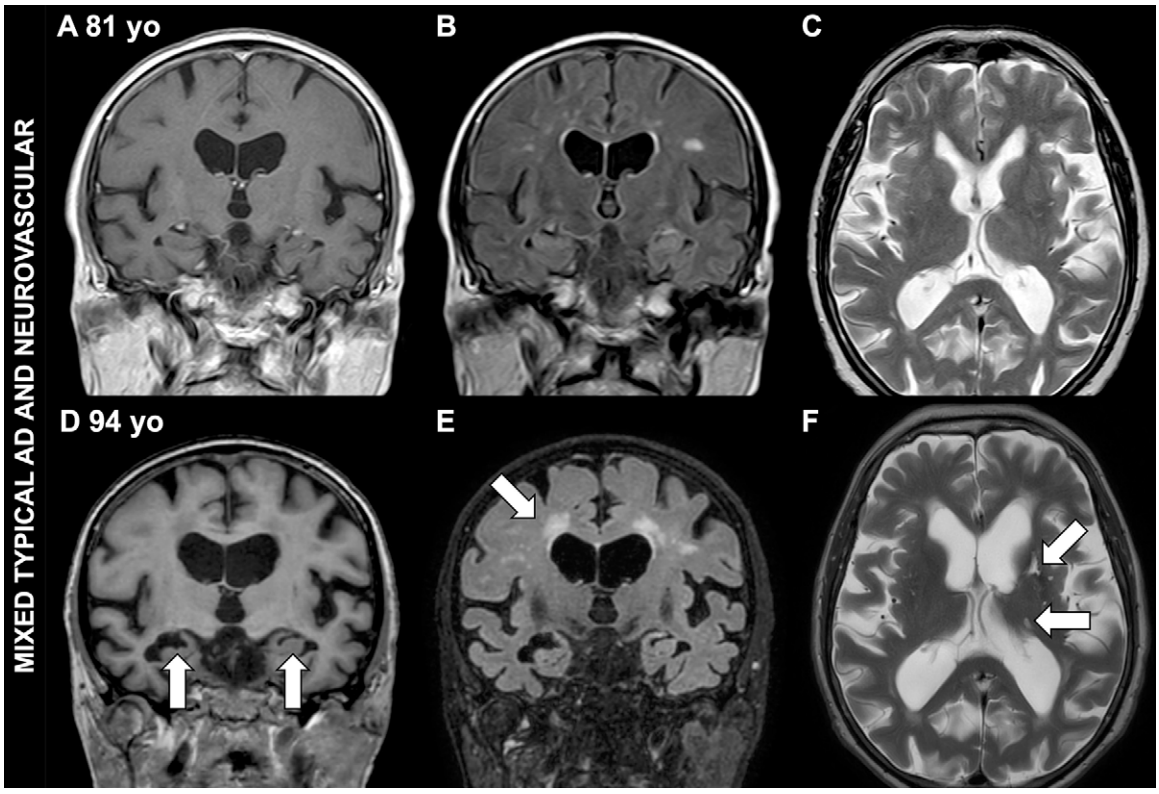

Figure 13: **(A–C)** Coronal T1-weighted **(A)**, coronal T2-weighted fluid-attenuated inversion recovery **(B)**, and axial T2-weighted **(C)** MRI scans in an 81-year-old female patient without cognitive complaints show no significant atrophy of the hippocampus and only beginning white matter hyperintensities. **(D–F)** Coronal T1-weighted **(D)**, coronal T2-weighted fluid-attenuated inversion recovery **(E)**, and axial T2-weighted **(F)** MRI scans in the same patient 13 years later show evidence of atrophy most pronounced in the right-dominant hippocampus (arrows in **D**), suggesting a component of typical Alzheimer disease (AD)–type neurodegeneration, associated with progressive white matter hyperintensities (arrow in **E**) and two minor infarcts of the left basal ganglia (arrows in **F**) that indicate a cerebrovascular disease component. This is a typical example of mixed neurodegenerative and cerebrovascular disease.

Genetic Subtypes and Genetic Risk Factors for FTD

Most cases of genetic FTD are due to mutations in one of the three following genes: *C9ORF72*, *MAPT*, or *GRN*. Rarely, genetic FTD is caused by a mutation in *TARDBP*, *VCP*, *CHMP2B*, *SQSTM1*, *UBQLN1*, or *TBK1*. Different mutations have different patterns of atrophy and clinical presentations, and different ages of presentation (31,47).

Normal Pressure Hydrocephalus Configuration and the Glymphatic System

The classic description of normal pressure hydrocephalus (NPH) includes the clinical triad of dementia, gait disturbance, and urinary incontinence. NPH is presumably related to impaired CSF dynamics. The radiologic findings associated with NPH include a dilated ventricular system with high-convexity tight sulci, transependymal transudation of CSF, dilation of the sylvian fissure, corpus callosum in a V-shaped angle in the coronal plan, posterior cingulate sulcus sign, and others. iNPH Radscale, a grading scale for the imaging findings of idiopathic NPH, summarizes key imaging findings (48). In some patients with suspected dementia, only some radiologic findings suggestive of NPH are present, yet without the full radiologic or clinical picture of NPH (Fig 11). It was recently suggested that radiologic NPH configuration, notably high-convexity tight sulci, represents a subgroup of non-AD pathophysiology associated with cognitive impairment, which may confound clinical and biomarker interpretation in AD clinical trials (49). Therefore, this NPH configuration is a potential explanation for cases not matching the aforementioned amyloid, tau, and neurodegeneration (ATN) model. If NPH configuration relates to impaired CSF dynamics and thus an impaired glymphatic system, it could be speculated that NPH configuration is a surrogate marker of an impaired glymphatic system. Under the simplified assumption that the glymphatic system is the "garbage" system of the brain, an impaired glymphatic system dynamic could result in an increased concentration of toxic substances around the brain, explaining the catalyst effect on brain degeneration.

Neuroradiologic NPH configuration does not imply a complete clinical picture of NPH (dementia, gait disturbance, and urinary incontinence) yet might be an imaging marker of impaired CSF flow and indicate a higher risk of subsequent cognitive decline. Likewise, moderate white matter hyperintensities do not imply the diagnosis of vascular dementia, but imply an increased risk of vascular cognitive impairment and risk of cognitive decline.

It has been suggested that dilated Virchow-Robin spaces can also be considered a marker of impaired CSF flow and surrogate marker of glymphatic system impairment. This

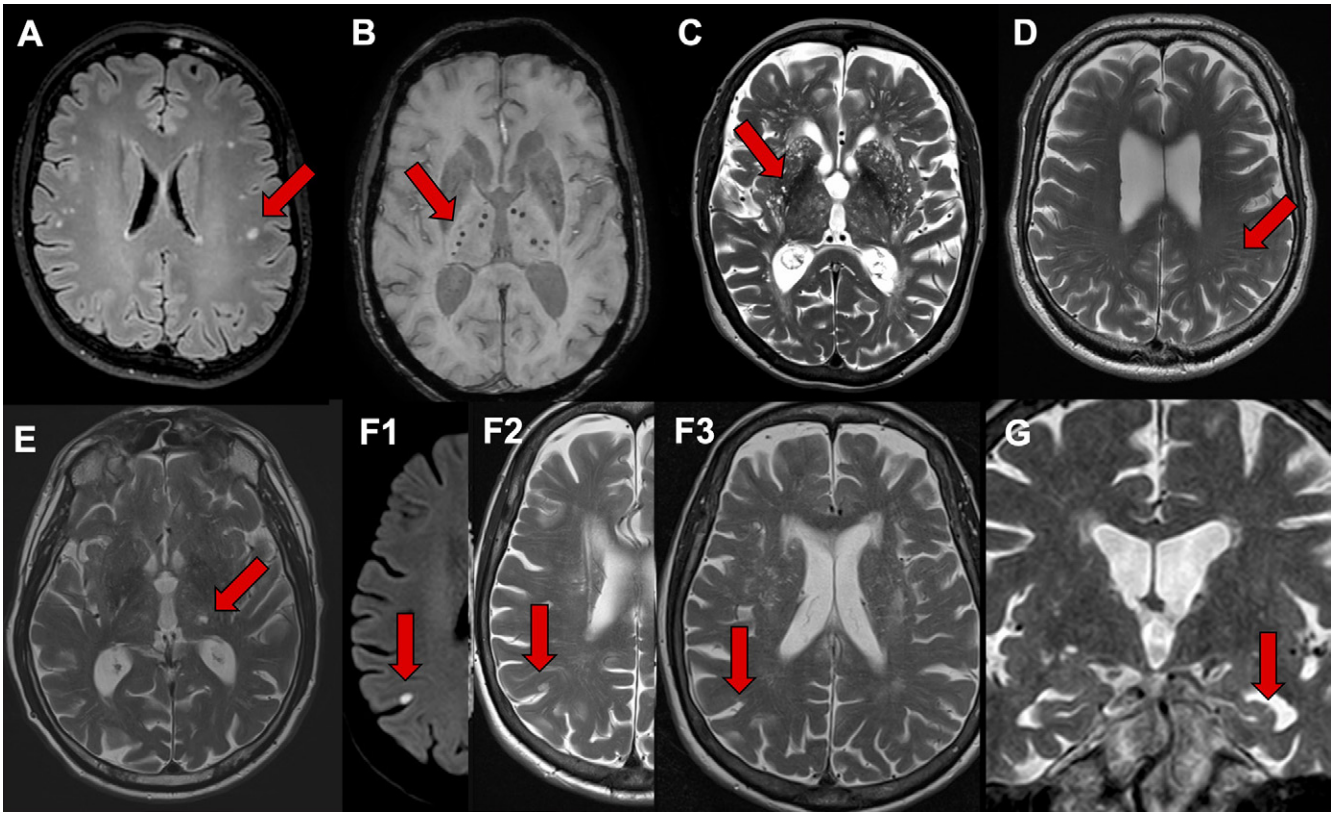

Figure 14: **(A–G)** Images show various MRI markers of cerebrovascular disease, including white matter hyperintensities/white matter lesions (arrow) on a T2-weighted fluid-attenuated inversion recovery image **(A)**; cerebral microbleeds (arrow) on a susceptibility-weighted image **(B)**; état criblé of the basal ganglia (arrow) on a T2-weighted image **(C)**; dilated perivascular spaces/Virchow-Robin spaces (arrow) on an axial T2-weighted image **(D)**; strategic lacune in the left thalamus (arrow) on a T2-weighted image **(E)**; cortical microinfarct (arrows in **F**) as an incidental finding on a diffusion-weighted image (*b* = 1000) **(F1)** and T2-weighted image **(F2)**, which is virtually invisible on a follow-up T2-weighted image 3 months later **(F3)**; and hippocampal microinfarct (arrow) on a T2-weighted image **(G)**.

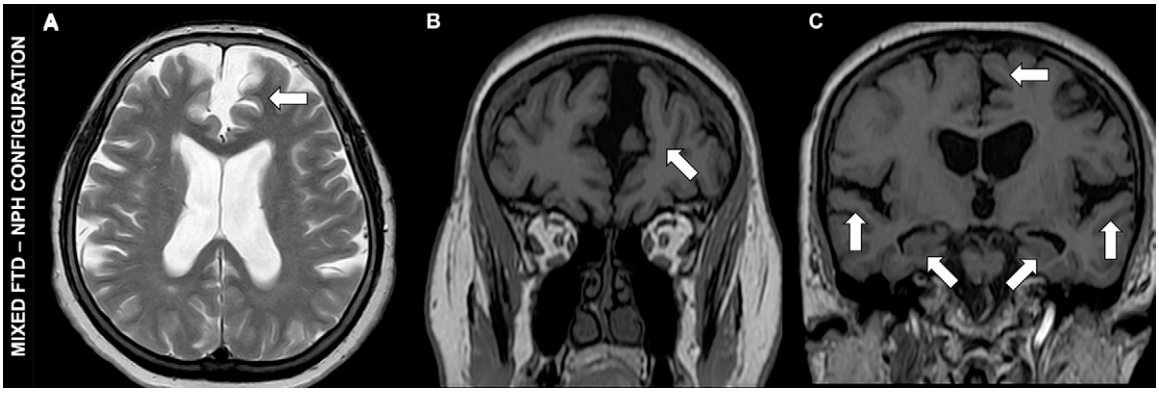

Figure 15: **(A, B)** Axial T2-weighted **(A)** and coronal T1-weighted **(B)** MRI scans in a 67-year-old female patient with progressive cognitive decline show left-dominant frontal atrophy (arrows). **(C)** Coronal T1-weighted MRI scan in the same patient shows several signs of normal pressure hydrocephalus (NPH) configuration (arrows), including a prominent ventricular system, insular enlargement, and crowding of the convexity sulci. In addition, there is beginning hippocampal atrophy as a feature of frontotemporal dementia (FTD), but this assessment is confounded by coexisting temporal horn enlargement as a feature of the NPH configuration. This example illustrates that it is not always possible to establish a firm radiologic diagnosis.

hypothesis that NPH configuration (and dilated Virchow-Robin spaces) might represent a neuroimaging marker for impaired CSF dynamics, which in turn indicates an impaired glymphatic system as a risk factor for neurodegeneration, is currently under investigation.

Of note, dilation of the temporal horns is a feature of NPH configuration. In the case of the coexistence of AD-related hippocampal atrophy and NPH configuration, the dilation of the temporal horns as a feature of NPH configuration may lead to a visual (radiologic) overestimation of the risk of hippocampal atrophy.

Other Rare Mimics of AD

Each case of hippocampal atrophy is not equivalent to AD. In addition to LATE, several other rare diseases exist that may lead to hippocampal atrophy. One example is a chronic stage

Table 1: Simplified Differential Diagnoses Based on Imaging Patterns

Imaging Finding	Associated Findings	Most Likely Diagnosis
Hippocampal atrophy		
Predominant hippocampal atrophy	Abnormal amyloid (amyloid PET, CSF, or blood markers)	Typical AD
Predominant hippocampal atrophy	Normal amyloid (amyloid PET, CSF, or blood markers), age >90 years, and tau markers	LATE
Asymmetric hippocampal atrophy and other, more pronounced atrophy	Predominant frontal atrophy, including hippocampal atrophy	Behavioral variant FTD
Asymmetric hippocampal atrophy and other, more pronounced atrophy	Predominant temporal pole atrophy (often asymmetric) and hippocampal atrophy	Semantic dementia (classic left, atypical right)
Asymmetric hippocampal atrophy and other, more pronounced atrophy	Predominant peri-insular atrophy, including hippocampal atrophy	Progressive nonfluent aphasia
Temporal horn enlargement mimicking hippocampal atrophy	Prominent ventricular system, crowding of sulci of vertex, corpus callosum in "V" configuration, posterior cingulate sulcus sign, dilation of sylvian fissure	Configuration of normal pressure hydrocephalus
Hippocampal atrophy and vascular imaging markers	Hippocampal atrophy and white matter hyperintensities, microbleeds, microinfarcts, strategic infarcts, dilated Virchow-Robin spaces	Mixed disease, AD and vascular dementia
Hippocampal atrophy and vascular imaging markers, notably lobar distribution of microbleeds	Hippocampal atrophy, lobar distribution of microbleeds (notably parieto-occipital), superficial siderosis, white matter signal anomaly	Mixed disease, AD and cerebral amyloid angiopathy
Hippocampal atrophy and signal abnormality	None	Hippocampal sclerosis
Hippocampal atrophy and signal abnormality	None	Status after limbic encephalitis
Predominant frontal atrophy		
Predominant frontal atrophy	Anterior-to-posterior gradient of atrophy, normal amyloid (amyloid PET, CSF, or blood markers)	Behavioral variant FTD
Predominant frontal atrophy	Abnormal amyloid (amyloid PET, CSF, or blood markers)	Frontal variant AD
Predominant frontal atrophy–temporal pole	Predominant temporal pole atrophy (often asymmetric) and hippocampal atrophy	Semantic dementia (classic left, atypical right [rtvFTD])
Predominant frontal atrophy–notably peri-insular	Predominant peri-insular atrophy, including hippocampal atrophy	Progressive nonfluent aphasia
Predominant parietal atrophy/PCA pattern		
Predominant parietal atrophy	Abnormal amyloid (amyloid PET, CSF, or blood markers)	Parietal variant AD
Predominant parietal atrophy	Abnormal dopamine nuclear medicine or abnormal nigrosome 1	Dementia with Lewy bodies
Predominant parietal atrophy	Abnormal dopamine nuclear medicine or abnormal nigrosome 1, cerebellar atrophy, movement disorder	Corticobasal degeneration
Predominant parietal atrophy	None	Normal variant

Note.—AD = Alzheimer disease, CSF = cerebrospinal fluid, FTD = frontotemporal dementia, LATE = limbic-predominant age-related TDP-43 encephalopathy, PCA = posterior cortical atrophy, rtv = right temporal variant.

after autoimmune encephalitis (limbic encephalitis) (50), which can be due to a variety of paraneoplastic (Fig 12) and nonparaneoplastic etiologies. Careful analysis of past medical history may provide clues in such cases.

Mixed and Overlapping Disease

Many instances of cognitive decline are related to a coexistence of diseases rather than an isolated neurodegenerative disease. The most common combination is AD-type neurodegeneration and cerebrovascular disease, particularly in older age (51). With advancing age, both pathologies may develop (Fig 13). Coexistent cerebrovascular disease is not always appreciated and is further discussed hereafter.

Cerebrovascular Disease, Vascular Cognitive Impairment, and Vascular Dementia

Isolated vascular dementia exists but is uncommon. More frequently, neurodegeneration and cerebrovascular disease coexist in older adults. Both diseases share risk factors, such as hypertension or high cholesterol. Importantly, if neurodegeneration and cerebrovascular disease coexist, the effect may be superadditive, meaning that one disease will function as a catalyst and accelerate the other (10).

Of note, while vascular dementia according to the strict definition is rare, it is very common to have mixed disease with a cerebrovascular disease component in addition to a neurodegenerative disease component.

Table 2: Simplified Differential Diagnoses Based on Key Clinical Findings

Key Clinical Finding	Most Likely Diagnosis
Predominant memory loss	
Hippocampal atrophy, abnormal amyloid (amyloid PET, CSF, or blood markers)	Typical AD
Hippocampal atrophy, normal amyloid (amyloid PET, CSF, or blood markers), age >90 years	LATE
Predominant frontal atrophy including hippocampal atrophy	Behavioral variant FTD
Vascular imaging markers (white matter hyperintensities, strategic infarcts, etc)	vascular cognitive impairment, vascular dementia
Prominent ventricular system, crowding of sulci of vertex, corpus callosum in "V" configuration, posterior cingulate sulcus sign, dilation of sylvian fissure	Normal pressure hydrocephalus
Hippocampal microinfarcts, often undetected at clinical MRI	Often missed diagnosis (sensitivity of clinical MRI is low)
Mixed imaging findings	Mixed disease
Predominant behavioral and executive function presentation	
Predominant frontal atrophy with anterior-to-posterior gradient that includes hippocampal atrophy, normal amyloid (amyloid PET, CSF, or blood markers)	Behavioral variant FTD
Predominant frontal atrophy with anterior to posterior gradient that includes hippocampal atrophy, abnormal amyloid (amyloid PET, CSF, or blood markers)	Frontal variant AD
Predominant language impairment	
Dominant left temporal pole atrophy, including asymmetric hippocampal atrophy	Semantic dementia
Dominant peri-insular atrophy, including asymmetric hippocampal atrophy	Progressive nonfluent aphasia
Dominant anterior peri-insular atrophy with anterior-to-posterior gradient, may include asymmetric hippocampal atrophy	Nonfluent/agrammatic primary progressive aphasia
Left-dominant peri-insular atrophy extending into parieto-occipital junction, may include asymmetric hippocampal atrophy	Logopenic variant primary progressive aphasia

Note.—AD = Alzheimer disease, CSF = cerebrospinal fluid, FTD = frontotemporal dementia, LATE = limbic-predominant age-related TDP-43 encephalopathy.

Criteria of Cerebrovascular Disease, Vascular Cognitive Impairment, and Vascular Dementia

The term *vascular cognitive impairment* is an umbrella term that includes the entire spectrum of vascular contributions to cognitive decline (52). The most severe degree, called vascular dementia, is at the extreme end of the vascular cognitive impairment spectrum (Fig S6). This presentation of patients with vascular cognitive impairment may differ from amnestic mild cognitive impairment, which often heralds AD.

Several criteria have been proposed for the definition of vascular dementia, the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences, or NINDS-AIREN, criteria being the most specific (53). Common to the various criteria is the objective of clinical research. Moreover, the definition of vascular dementia is, in general, strict. Those criteria were not initially intended for daily clinical use and the threshold for the definition of vascular dementia is high, while definitions for earlier stages of cerebrovascular disease within the vascular cognitive impairment spectrum are lacking. This might be one of the reasons for lack of appreciation of cerebrovascular disease in suspected dementia or cognitive impairment.

MRI Markers of Cerebrovascular Disease

MRI has the advantage of providing several markers of cerebrovascular disease in one imaging session (54). This advantage of MRI might also be a weakness. An individual case typically has various MRI markers of cerebrovascular disease. It is difficult to decide what burden of vascular disease contributes to cognitive impairment, given that vascular pathology, such as white matter hyperintensities, are common in "normal" brain aging. Consequently, there is a large variability in the radiologic reporting of the various MRI markers of cerebrovascular disease.

Cerebrovascular Disease Subtypes

There is substantial interindividual variability of cerebrovascular disease that includes cerebral small vessel disease, cerebral large vessel disease, single or multiple lacunes (small cystic cavities of brain substance as the chronic stage of an ischemic infarction), and there are variable patterns in the expression of MRI markers of cerebrovascular disease. In analogy to the other forms of dementia discussed herein, those different patterns might be considered as cerebrovascular disease subtypes.

White Matter Hyperintensities

White matter hyperintensities are markers of cerebral small vessel disease (Fig 14A). They are often semiquantitatively described using the Fazekas score (0–3) (55), and generally increase with age and indicate a higher risk of stroke and cognitive decline. After the age of 40 years, the majority of individuals (>90%) will harbor some degree of white matter pathology, which, when low in burden, does not necessarily lead to cognitive deficits. Apart from white matter hyperintensity burden, there is increasing evidence of an association between the location of white matter hyperintensities and functional outcomes. In the future, it is expected that age- and sex-specific reference curves and strategic lesion location maps will better inform clinical practice regarding the clinical impact of white matter hyperintensities.

Microbleeds

Cerebral microbleeds are small punctiform lesions best appreciated at susceptibility-weighted imaging (41) (Fig 14B). They are associated with aging and cognitive decline. A deep location may suggest hypertension. In contrast, a superficial lobar distribution is indicative of cerebral amyloid angiopathy (CAA), which may be associated with AD more frequently than a simple co-occurrence of CAA, suggesting an interaction between CAA and AD (56). However, lobar cerebral microbleeds are only found in 20%–30% of AD cases and their absence does not rule out AD.

Enlarged Perivascular Spaces

Enlarged perivascular spaces, also known as dilated Virchow-Robin spaces, recently emerged as a potential marker of cerebrovascular disease (Fig 14D). Possible underlying mechanisms include hypertension, obstruction, and inflammation (57). Dilated Virchow-Robin spaces are also associated with cerebral amyloid angiopathy (58–60). At a group level, enlarged perivascular spaces probably represent an emerging cerebrovascular marker; however, there is normal interindividual variability, with frequent observation of enlarged perivascular spaces also in younger adults. Thus, it remains unclear how important this probable cerebrovascular disease marker is at an individual level in the context of cognitive decline.

État Criblé

État criblé refers to a special type of enlarged perivascular spaces at the level of the basal ganglia (Fig 14C). In contrast to the general enlarged perivascular spaces (typically of the hemispheres) discussed in the previous paragraph, état criblé is probably a more direct and important cerebrovascular disease marker and almost invariably associated with confluent white matter hyperintensities.

Strategic Lacunes

According to the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria (53), strategic lacunes are lacunes in the basal ganglia (Fig 14E). T2-weighted MRI sequences can better visualize strategic lacunes in the thalami than T2 fluid-attenuated inversion recovery (FLAIR) sequences. The lacunes are often missed with the FLAIR sequence in this location (61).

Cortical Microinfarcts

Cortical microinfarcts have recently emerged as a cerebrovascular disease biomarker and, when recent, can be detected as incidental findings at diffusion imaging (Fig 14F1, 14F2). If imaging is performed when restricted diffusion is not present, it may be difficult or even impossible to detect such cortical microinfarcts (Fig 14F3). While the detection rate of chronic cortical microinfarcts is good at 7 T, a substantial number of chronic cortical microinfarcts remain undetected at 3 T in a clinical setting (62,63).

Hippocampal Microinfarcts

Hippocampal microinfarcts are a subtype of cortical microinfarcts (Fig 14G). At histopathologic assessment, hippocampal microinfarcts are quite common in older adults and may be associated with cognitive decline, mimicking AD. It is notoriously difficult to detect hippocampal microinfarcts. For example, a recent study investigating postmortem MRI at 3 T (compared with imaging parameters equivalent to clinical MRI) observed an accuracy of 2% to detect hippocampal microinfarcts (64). This might explain why this important cerebrovascular disease marker is likely highly underestimated.

Other Forms of Overlapping or Mixed Disease

Another important overlap is between AD and cerebral amyloid angiopathy, recently defined in the Boston 2.0 criteria (60). Both diseases are linked to amyloid accumulation, although it is not the same type of amyloid and not the same compartment of accumulation (65). Nevertheless, there is a coexistence of AD and cerebral amyloid angiopathy that clearly exceeds chance, indicating an interaction between the two diseases, with the *APOEE4* allele increasing the risk for both. This is of particular importance in view of the aforementioned side effects of newly emerging antiamyloid therapies (amyloid-related imaging abnormalities due to brain edema [ARIA-E] and hemosiderin deposits [ARIA-H]), which are thought to occur more often in individuals who also harbor vascular amyloid pathology (eg, as evidenced by presences of multiple lobar microbleeds). While the overlapping or mixed disease of AD and cerebrovascular disease and AD and cerebral amyloid angiopathy are important examples, other coexistences of neurodegenerative and cerebrovascular diseases exist (66–68) (Fig 5B). Thus, it is important to avoid trying to force a single disease label on an individual patient, as this deprives them of receiving adequate prognostic counseling, symptom-reducing treatment, or, in the case of cerebrovascular disease, preventive management. Given the frequent coexistence of vascular and neurodegenerative pathologies, radiologists have a key role to signal dual disease. It is also important to highlight that sometimes, due to the coexistence of several imaging markers suggesting overlapping or mixed disease, it may be impossible to establish a firm diagnosis based on radiologic assessment (Fig 15).

Other Diseases

A variety of other diseases and conditions may cause cognitive decline and dementia. These include subdural hematoma, neoplasm,

infection and/or inflammation such as with Creutzfeldt–Jakob disease, neurodegeneration with brain iron accumulation, and metabolic or toxic diseases. Such conditions are not neurodegenerative diseases in the strict sense and are out of the scope of the current review.

Differential Diagnosis Based on Imaging Findings and Clinical Symptoms

The various forms of dementia discussed herein have partially overlapping and partially distinct patterns of atrophy and clinical presentations. Simplified differential diagnoses based on imaging patterns are summarized in Table 1. Simplified differential diagnoses based on key clinical findings are summarized in Table 2.

Conclusion

Dementia is more than typical Alzheimer disease (AD), and AD is more than a single and stereotypical process of neurocognitive decline. Each patient will have a personal blend of different components of neurodegenerative and cerebrovascular diseases. Neuroimaging, in concert with genetic and laboratory testing, should aim for early diagnosis—ideally before the onset of clinically evident dementia—with subtyping of AD and other forms of dementia and with consideration for coexisting disease. This will be the fundamental basis to better understand the mechanisms of AD, and to aid the development of individualized and efficient therapies.

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References

1. Ghezzi L, Scarpini E, Galimberti D. Disease-modifying drugs in Alzheimer's disease. Drug Des Devel Ther 2013;7:1471–1478.
2. Sevigny J, Chiao P, Bussière T, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 2016;537(7618):50–56. [Published correction appears in Nature 2017;546(7659):564.]
3. Bateman RJ, Cummings J, Schobel S, et al. Gantenerumab: an anti-amyloid monoclonal antibody with potential disease-modifying effects in early Alzheimer's disease. Alzheimers Res Ther 2022;14(1):178.
4. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med 2023;388(1):9–21.
5. Barakos J, Purcell D, Suhy J, et al. Detection and Management of Amyloid-Related Imaging Abnormalities in Patients with Alzheimer's Disease Treated with Anti-Amyloid Beta Therapy. J Prev Alzheimers Dis 2022;9(2):211–220.
6. Cogswell PM, Barakos JA, Barkhof F, et al. Amyloid-Related Imaging Abnormalities with Emerging Alzheimer Disease Therapeutics: Detection and Reporting Recommendations for Clinical Practice. AJNR Am J Neuroradiol 2022;43(9):E19–E35.
7. Adhikari UK, Khan R, Mikhael M, et al. Therapeutic anti-amyloid β antibodies cause neuronal disturbances. Alzheimers Dement 2022. 10.1002/alz.12833. Published online December 14, 2022.
8. Reish NJ, Jamshidi P, Stamm B, et al. Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke. N Engl J Med 2023;388(5):478–479.
9. Tomlinson BE, Blessed G, Roth M. Observations on the brains of non-demented old people. J Neurol Sci 1968;7(2):331–356.
10. Haller S, Barkhof F. Interaction of Vascular Damage and Alzheimer Dementia: Focal Damage and Disconnection. Radiology 2017;282(2):311–313.
11. Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med 2010;362(4):329–344.
12. Gowda P, Reddy PH, Kumar S. Deregulated mitochondrial microRNAs in Alzheimer's disease: Focus on synapse and mitochondria. Ageing Res Rev 2022;73:101529.
13. Jack CR Jr, Bennett DA, Blennow K, et al; Contributors. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14(4):535–562.
14. Dodich A, Mendes A, Assal F, et al. The A/T/N model applied through imaging biomarkers in a memory clinic. Eur J Nucl Med Mol Imaging 2020;47(2):247–255.
15. Crutch SJ, Lehmann M, Schott JM, Rabinovici GD, Rossor MN, Fox NC. Posterior cortical atrophy. Lancet Neurol 2012;11(2):170–178.
16. Johnson JK, Head E, Kim R, Starr A, Cotman CW. Clinical and pathological evidence for a frontal variant of Alzheimer disease. Arch Neurol 1999;56(10):1233–1239.
17. Rohrer JD, Schott JM. Primary progressive aphasia: defining genetic and pathological subtypes. Curr Alzheimer Res 2011;8(3):266–272.
18. Frankó E, Joly O; Alzheimer's Disease Neuroimaging Initiative. Evaluating Alzheimer's disease progression using rate of regional hippocampal atrophy. PLoS One 2013;8(8):e71354.
19. Villemagne VL, Barkhof F, Garibotto V, Landau SM, Nordberg A, van Berckel BNM. Molecular Imaging Approaches in Dementia. Radiology 2021;298(3):517–530.
20. Ossenkoppele R, Pichet Binette A, Groot C, et al. Amyloid and tau PET-positive cognitively unimpaired individuals are at high risk for future cognitive decline. Nat Med 2022;28(11):2381–2387.
21. Ten Kate M, Ingala S, Schwarz AJ, et al. Secondary prevention of Alzheimer's dementia: neuroimaging contributions. Alzheimers Res Ther 2018;10(1):112.
22. Collij LE, Salvadó G, Wottschel V, et al; Alzheimer's Disease Neuroimaging Initiative; for the ALFA study. Spatial-Temporal Patterns of β-Amyloid Accumulation: A Subtype and Stage Inference Model Analysis. Neurology 2022;98(17):e1692–e1703. [Published correction appears in Neurology 2022:10.1212/WNL.0000000000201144.]
23. Vogel JW, Young AL, Oxtoby NP, et al; Alzheimer's Disease Neuroimaging Initiative. Four distinct trajectories of tau deposition identified in Alzheimer's disease. Nat Med 2021;27(5):871–881.
24. Naj AC, Jun G, Reitz C. Effects of multiple genetic loci on age at onset in late-onset Alzheimer disease: a genome-wide association study. JAMA Neurol 2014;71(11):1394–1404. [Published correction appears in JAMA Neurol 2014;71(11):1457.]
25. Jansen WJ, Ossenkoppele R, Knol DL, et al; Amyloid Biomarker Study Group. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 2015;313(19):1924–1938.
26. Reiman EM, Arboleda-Velasquez JF, Quiroz YT, et al; Alzheimer's Disease Genetics Consortium. Exceptionally low likelihood of Alzheimer's dementia in APOE2 homozygotes from a 5,000-person neuropathological study. Nat Commun 2020;11(1):667.
27. Bateman RJ, Xiong C, Benzinger TL, et al; Dominantly Inherited Alzheimer Network. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 2012;367(9):795–804.
28. Teunissen CE, Verberk IMW, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. Lancet Neurol 2022;21(1):66–77.
29. Crutch SJ, Schott JM, Rabinovici GD, et al; Alzheimer's Association ISTAART Atypical Alzheimer's Disease and Associated Syndromes Professional Interest Area. Consensus classification of posterior cortical atrophy. Alzheimers Dement 2017;13(8):870–884.
30. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology 2011;76(11):1006–1014.
31. Warren JD, Rohrer JD, Rossor MN. Clinical review. Frontotemporal dementia. BMJ 2013;347:f4827.
32. Niedowicz DM, Nelson PT, Murphy MP. Alzheimer's disease: pathological mechanisms and recent insights. Curr Neuropharmacol 2011;9(4):674–684.
33. Rabinovici GD, Carrillo MC, Forman M, et al. Multiple comorbid neuropathologies in the setting of Alzheimer's disease neuropathology and implications for drug development. Alzheimers Dement (N Y) 2016;3(1):83–91.
34. Nelson PT, Dickson DW, Trojanowski JQ, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. Brain 2019;142(6):1503–1527.
35. Weil RS, Lashley TL, Bras J, Schrag AE, Schott JM. Current concepts and controversies in the pathogenesis of Parkinson's disease dementia and Dementia with Lewy Bodies. F1000 Res 2017;6:1604.
36. Orme T, Guerreiro R, Bras J. The Genetics of Dementia with Lewy Bodies: Current Understanding and Future Directions. Curr Neurol Neurosci Rep 2018;18(10):67.

37. Mak E, Su L, Williams GB, et al. Differential Atrophy of Hippocampal Subfields: A Comparative Study of Dementia with Lewy Bodies and Alzheimer Disease. Am J Geriatr Psychiatry 2016;24(2):136–143.
38. Schwarz ST, Afzal M, Morgan PS, Bajaj N, Gowland PA, Auer DP. The 'swallow tail' appearance of the healthy nigrosome - a new accurate test of Parkinson's disease: a case-control and retrospective cross-sectional MRI study at 3T. PLoS One 2014;9(4):e93814.
39. Haller S, Fällmar D, Larsson EM. Susceptibility weighted imaging in dementia with Lewy bodies: will it resolve the blind spot of MRI? Neuroradiology 2016;58(2):217–218.
40. Shams S, Fällmar D, Schwarz S, et al. MRI of the Swallow Tail Sign: A Useful Marker in the Diagnosis of Lewy Body Dementia? AJNR Am J Neuroradiol 2017;38(9):1737–1741.
41. Haller S, Haacke EM, Thurnher MM, Barkhof F. Susceptibility-weighted Imaging: Technical Essentials and Clinical Neurologic Applications. Radiology 2021;299(1):3–26.
42. Haller S, Davidsson A, Tisell A, Ochoa-Figueroa M, Georgiopoulos C. MRI of nigrosome-1: A potential triage tool for patients with suspected parkinsonism. J Neuroimaging 2022;32(2):273–278.
43. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 2017;89(1):88–100.
44. McKeith I, O'Brien J, Walker Z, et al; DLB Study Group. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. Lancet Neurol 2007;6(4):305–313.
45. Kantarci K, Lowe VJ, Chen Q, et al. β-Amyloid PET and neuropathology in dementia with Lewy bodies. Neurology 2020;94(3):e282–e291.
46. Snowden JS. Changing perspectives on frontotemporal dementia: A review. J Neuropsychol 2022. 10.1111/jnp.12297. Published online October 31, 2022.
47. Sivasathiaseelan H, Marshall CR, Agustus JL, et al. Frontotemporal Dementia: A Clinical Review. Semin Neurol 2019;39(2):251–263.
48. Kockum K, Lilja-Lund O, Larsson EM, et al. The idiopathic normal-pressure hydrocephalus Radscale: a radiological scale for structured evaluation. Eur J Neurol 2018;25(3):569–576.
49. Graff-Radford J, Gunter JL, Jones DT, et al. Cerebrospinal fluid dynamics disorders: Relationship to Alzheimer biomarkers and cognition. Neurology 2019;93(24):e2237–e2246.
50. Miller TD, Chong TT, Aimola Davies AM, et al. Focal CA3 hippocampal subfield atrophy following LGI1 VGKC-complex antibody limbic encephalitis. Brain 2017;140(5):1212–1219.
51. Schneider JA, Bennett DA. Where vascular meets neurodegenerative disease. Stroke 2010;41(10 Suppl):S144–S146.
52. van der Flier WM, Skoog I, Schneider JA, et al. Vascular cognitive impairment. Nat Rev Dis Primers 2018;4(1):18003.
53. van Straaten EC, Scheltens P, Knol DL, et al. Operational definitions for the NINDS-AIREN criteria for vascular dementia: an interobserver study. Stroke 2003;34(8):1907–1912.
54. Smith EE, Biessels GJ, De Guio F, et al. Harmonizing brain magnetic resonance imaging methods for vascular contributions to neurodegeneration. Alzheimers Dement (Amst) 2019;11(1):191–204.
55. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987;149(2):351–356.
56. Haller S, Vernooij MW, Kuijer JPA, Larsson EM, Jäger HR, Barkhof F. Cerebral Microbleeds: Imaging and Clinical Significance. Radiology 2018;287(1):11–28.
57. Adams HH, Hilal S, Schwingenschuh P, et al. A priori collaboration in population imaging: The Uniform Neuro-Imaging of Virchow-Robin Spaces Enlargement consortium. Alzheimers Dement (Amst) 2015;1(4):513–520.
58. Charidimou A, Boulouis G, Pasi M, et al. MRI-visible perivascular spaces in cerebral amyloid angiopathy and hypertensive arteriopathy. Neurology 2017;88(12):1157–1164.
59. Martinez-Ramirez S, van Rooden S, Charidimou A, et al. Perivascular Spaces Volume in Sporadic and Hereditary (Dutch-Type) Cerebral Amyloid Angiopathy. Stroke 2018;49(8):1913–1919.
60. Charidimou A, Boulouis G, Frosch MP, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. Lancet Neurol 2022;21(8):714–725.
61. Bastos Leite AJ, van Straaten EC, Scheltens P, Lycklama G, Barkhof F. Thalamic lesions in vascular dementia: low sensitivity of fluid-attenuated inversion recovery (FLAIR) imaging. Stroke 2004;35(2):415–419.
62. van Veluw SJ, Zwanenburg JJ, Rozemuller AJ, Luijten PR, Spliet WG, Biessels GJ. The spectrum of MR detectable cortical microinfarcts: a classification study with 7-tesla postmortem MRI and histopathology. J Cereb Blood Flow Metab 2015;35(4):676–683.
63. van Veluw SJ, Hilal S, Kuijf HJ, et al. Cortical microinfarcts on 3T MRI: Clinical correlates in memory-clinic patients. Alzheimers Dement 2015;11(12):1500–1509.
64. Scheffler M, Salomir R, Maturana E, Montandon ML, Kövari EV, Haller S. Identification of hippocampal cortical microinfarcts on postmortem 3-T magnetic resonance imaging. Neuroradiology 2021;63(9):1569–1573.
65. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease - one peptide, two pathways. Nat Rev Neurol 2020;16(1):30–42.
66. Piazza F, Greenberg SM, Savoiardo M, et al. Anti-amyloid β autoantibodies in cerebral amyloid angiopathy-related inflammation: implications for amyloid-modifying therapies. Ann Neurol 2013;73(4):449–458.
67. Sperling RA, Jack CR Jr, Black SE, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement 2011;7(4):367–385.
68. Carlson C, Estergard W, Oh J, et al. Prevalence of asymptomatic vasogenic edema in pretreatment Alzheimer's disease study cohorts from phase 3 trials of semagacestat and solanezumab. Alzheimers Dement 2011;7(4):396–401.