Neuroimaging in Dementia

48

A Clinical Approach

Sven Haller and Frederik Barkhof

Contents

This publication is endorsed by: European Society of Neuroradiology (www.esnr.org).

S. Haller (✉)
CIRD – Centre d'Imagerie Rive Droite,
Geneva, Switzerland

Department of Surgical Sciences, Radiology,
Uppsala University, Uppsala, Sweden

Faculty of Medicine, University of Geneva,
Geneva, Switzerland
e-mail: sven.haller@gmail.com

F. Barkhof
Department of Radiology and Nuclear Medicine,
VU University Medical Centre (VUmc), Amsterdam,
The Netherlands

UCL Institutes of Biomedical Engineering and Neurology,
London, UK
e-mail: f.barkhof@vumc.nl; f.barkhof@ucl.ac.uk

F. Barkhof et al. (eds.), *Clinical Neuroradiology*,
https://doi.org/10.1007/978-3-319-68536-6_64

Abstract

Dementia is not a diagnosis or a specific disease entity but a syndrome that describes a wide range of symptoms leading to a decline in mental ability severe enough to interfere with daily life.

Neurodegenerative disorders including dementing disorders and movement disorders may present with overlapping clinical symptoms. Likewise, the underlying molecular and cellular pathology may be overlapping. Consequently, dementia syndromes and movement disorders may be considered as a spectrum of diseases, and symptoms may vary over time. Moreover, there is no direct link between clinical symptoms and imaging findings: the same degree of brain atrophy or metabolic abnormality may be associated to a variable degree of cognitive impairment, or from the other perspective, the same degree of cognitive impairment may be associated with variable level of brain atrophy or metabolic abnormality. Finally, it is not uncommon to have coexisting pathology, for example, Alzheimer type neurodegeneration and a vascular contribution.

In the first part, we review basic clinical presentations of dementia syndromes. In the second part, we review the ***radiological techniques*** and typical ***clinical neuroradiology*** findings of the various types of dementia, including Alzheimer dementia (hippocampal atrophy, hypometabolism/hypoperfusion in posterior cingulate and bilateral parietal areas), vascular dementia (small and large vessel disease), fronto-temporal lobar degeneration (fronto-temporal/peri-insular atrophy and hypometabolism/hypoperfusion), and dementia with Lewy Bodies (reduced dopamine uptake in striatum, abnormality of the nigrosome1). Additionally, we review unusual clinical presentations of dementia, including young-onset dementia and rapidly progressive dementia. Finally, we briefly discuss the overlapping clinical presentation and underlying pathology between dementia and movement disorders.

Keywords

Neuroimaging · Dementia · Atrophy · Alzheimer · Cognitive decline; Mild cognitive impairment

Abbreviations	
AD	Alzheimer disease
ASL	Arterial spin labeling
bvFTD	Behavioral variant fronto-temporal dementia
CAA	Cerebral amyloid angiopathy
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CBD	Corticobasal disease
CBS	Corticobasal syndrome
CJD	Creutzfeldt-Jakob disease
CMB	Cerebral microbleeds
CTE	Chronic traumatic encephalopathy
DAT	Dopamine transporter
DLB	Dementia with Lewy bodies
FDG	Fluoro-deoxy-glucose
FTD	Frontotemporal dementia
FTLD	Fronto-temporal lobar degeneration
LVD	Large vessel disease
MCI	Mild cognitive impairment
MSA	Multisystem atrophy
MSA-c	MSA cerebellar type
MSA-p	MSA Parkinsonian type
PCA	Posterior cortical atrophy
PCC	Posterior cingulate cortex
PD	Parkinson disease
PNFA	Progressive nonfluent aphasia
PPA	Primary progressive aphasia
PSP	Progressive supranuclear palsy
SD	Semantic dementia
SVD	Small vessel disease
VaD	Vascular dementia
WMH	White matter hyperintensities

Introduction

Dementia is not a diagnosis or specific disease but a general syndrome that describes a wide range of symptoms leading to a decline in mental ability severe enough to interfere with daily life. Progressive decline in memory is the archetypical symptom, but other symptoms include reduced attention, altered behavior or speech, and the inability to perform everyday activities. These symptoms typically progressively increase over time, yet a certain degree of fluctuation, is oftentimes observed, i.e., some days are better than others.

As discussed in ▶ Chap. 46, "Neurodegenerative Disorders: Classification and Imaging Strategy," there is overlap between dementia and movement disorders, for example, between dementia with Lewy bodies (DLB) and Parkinson disease (PD). The first part of this chapter discusses typical presentation patterns of dementia syndromes. The second part reviews the most common types of dementia. The typical types of movement disorders will be discussed in ▶ Chap. 49, "Neuroimaging in Movement Disorders."

Clinical Presentation of Dementia and Patterns of Pathology

Progressive memory loss is an evident clinical manifestation of dementia. It is however essential to emphasize that not all types of dementia have progressive memory loss as the leading clinical symptom, notably at early stages of the neurodegenerative disease progress. Other clinical symptoms of dementia include language impairment, disorientation, mood disbalance, visual symptoms, slowness of movement, and executive impairment (Table 1).

Progressive Memory Loss

Progressive memory loss is the most common presentation of dementia. In particular in the elderly, progressive memory loss is in most cases due to AD type pathology, oftentimes associated with some degree of microvascular disease, due to the high prevalence and partly overlapping risk factors of both conditions. In the younger population below 65, in particular FTLD variants are relatively more common, although in absolute numbers AD type pathology remains the most frequent origin. Evidently each type of dementia, including also VaD and DLB, can present with initial progressive memory loss.

Table 1 Clinical modes of presentations in dementia

Symptoms	Typical	Also occurs in
Short-term memory loss and encoding difficulties	Typical AD	FTLD, VaD, DLB
Progressive decline in visuospatial or visuoperceptual skills, literacy, and praxis	PCA due to AD	DLB, CBD
Language impairment/ progressive aphasia	FTLD, notably SD and PNFA, PPA	Variants of AD, DLB, VaD
Frontal/ dysexecutive	bvFTD	Frontal variant AD
Early onset dementia	Young-onset AD, FTLD	Occupational (solvents), genetic e.g., CADASIL
Rapidly progressive dementia	CJD	Toxic, metabolic, neoplasm, other

For abbreviations, see list at beginning of chapter

Behavioral/Dysexecutive Predominant Presentation

Behavioral changes or a dysexecutive predominant presentation are in most cases due to FTLD pathology, yet can also be caused by variants of AD pathology, notably behavioral presentation of AD, dysexecutive presentation of AD combined behavioral/dysexecutive presentation of AD.

Language Dominant Presentations

Language predominant presentation can be due to a variety of underlying pathologies. Primary progressive aphasia (PPA) is primarily a clinical classification. PPA can be further divided into

- Nonfluent/Agrammatic Variant, also referred to as "nonfluent progressive aphasia" or "progressive nonfluent aphasia" (PNFA)
- Semantic variant = "semantic dementia" (SD)
- Logopenic variant, also referred to as "logopenic progressive aphasia" or "progressive mixed aphasia"

The first two entities belong to the group of FTLD, while the latter variant generally has an underlying AD pathology.

Posterior Cortical Atrophy (PCA)

Posterior cortical atrophy (PCA) is characterized by a progressive disruption of complex visual processing related to neurodegeneration in posterior brain areas (parietal and occipital lobes). In most cases, PCA is due to AD pathology (often with a younger age of onset), yet it may also be due to DLB or CBD pathology. No specific demographic has been identified as being particularly at risk and no genetic linkages have been established. Atrophy on imaging is in general more pronounced in bilateral parieto-occipital and temporo-occipital regions, sometimes more pronounced on the right hemisphere, and associated with hypometabolism on FDG PET in the same areas (Figs. 1 and 2).

Early-Onset Dementia

Early-onset dementia is in the majority of cases still due to AD pathology, even though FTLD pathology is relatively more common in the younger patient population (Rossor et al. 2010). Most common causes of early-onset dementia are summarized in Table 2.

Rapidly Progressive Dementia

Rapidly progressive dementia can be caused by a variety neurodegenerative, toxic/metabolic, infectious, autoimmune, neoplastic, and other conditions. The wide differential diagnosis in patients with rapidly progressive (Paterson et al. 2012) warrants extensive serologic, immunologic, and CSF analysis. The MRI protocol should include DWI and gadolinium administration.

As an important example of rapidly progressive dementia, we briefly review prion disease and

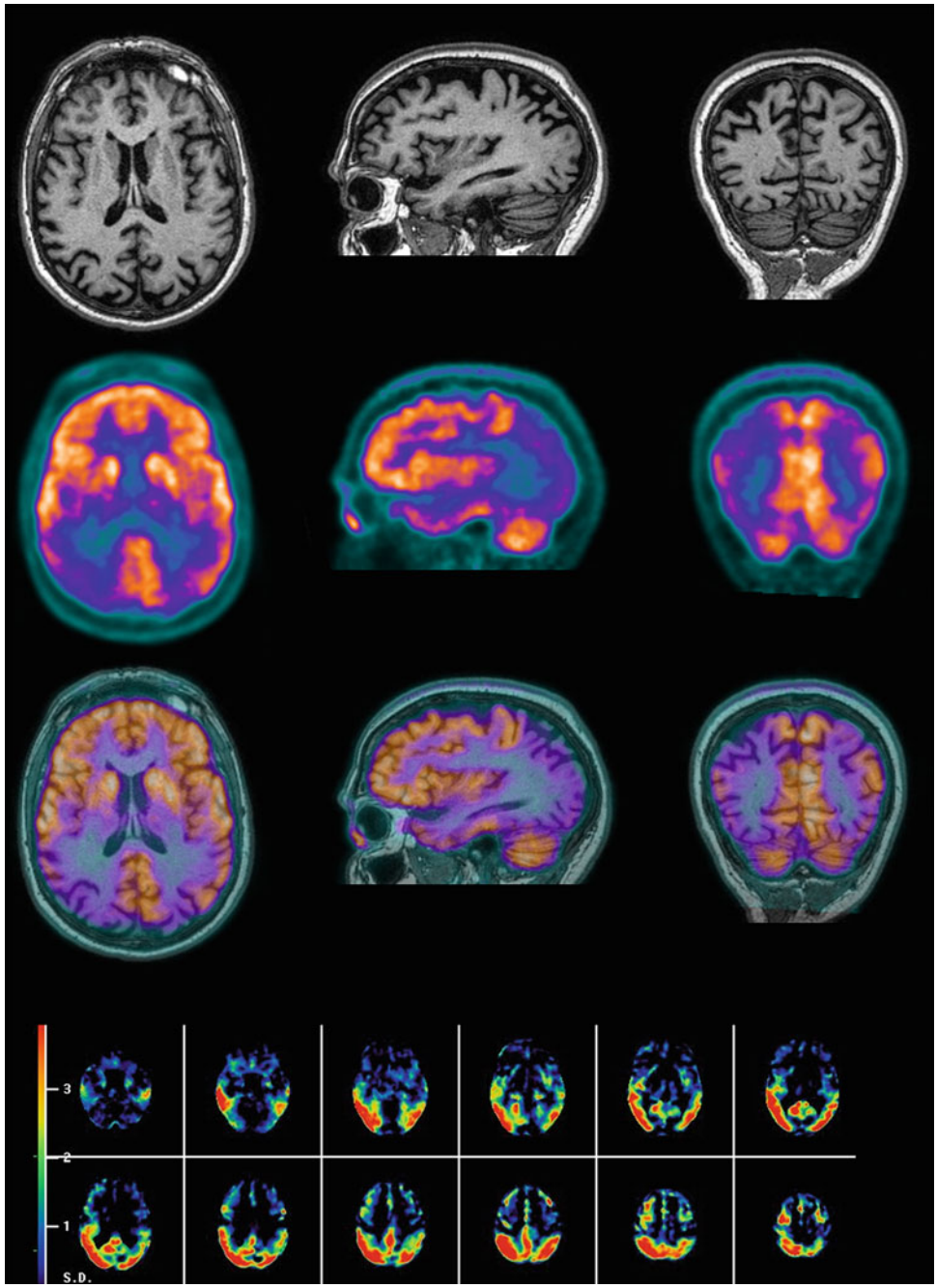

Fig. 1 T1w 3D MR images (first row), FDG PET images (second row), and fused PET-MRI images (third row) in a patient with a clinical diagnosis of PCA, showing an atrophy in parieto-occipital cortex and a more extensive parieto-occipital hypometabolism. The two lower rows indicate the topography of hypometabolism on the FDG PET images, in the comparison of the individual image to a normal reference database (BRASS, Hermes medical solutions, Stockholm, Sweden)

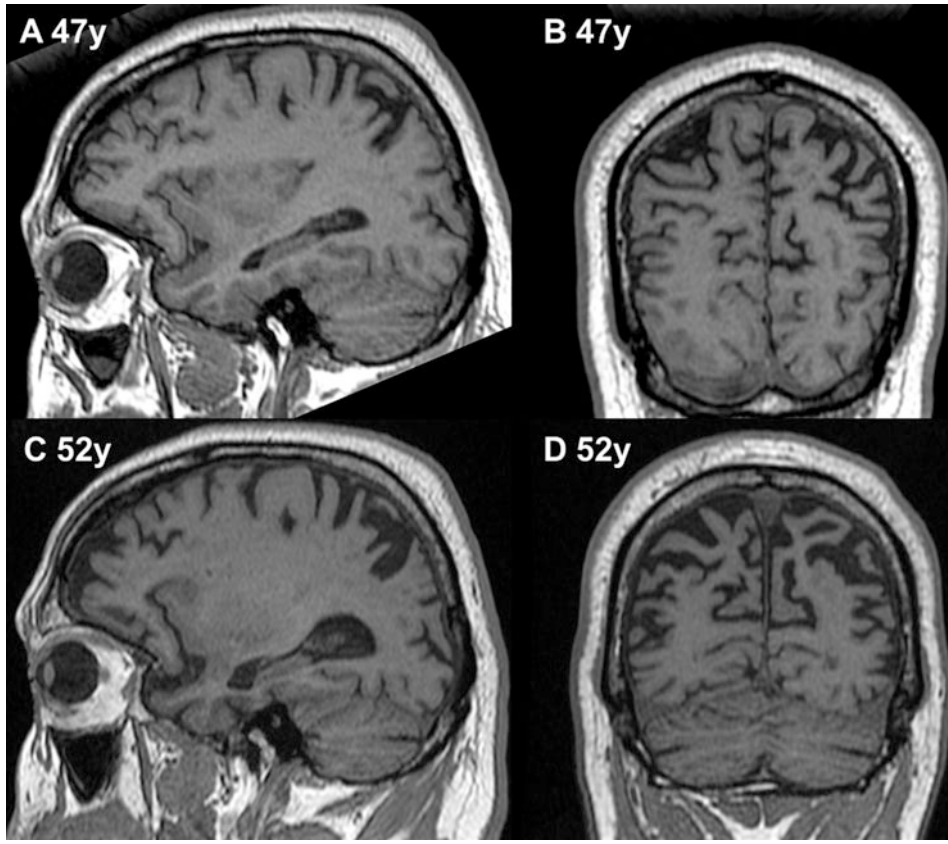

Fig. 2 Progression of PCA in a male patient from age 47 Koedams score 1 (**a**, sagittal T1w, **b** coronal T1w) to age 52 with Koedam score 2 (**c**, sagittal T1w, **d** coronal T1w)

Table 2 Overview of common cases of early-onset dementia

	Clinical presentation	Genetics
AD 34%	In general, similar to typical (sporadic) AD, though more often myoclonus, relative preservation of naming, sometimes prominent speech production deficits	Amyloid precursor protein (APP), presenilin-1 and presenilin-2 (PSEN1 and PSEN2) in small subset of patients; most sporadic
VaD 18%	Vascular changes common in the elderly, yet relatively uncommon in the younger Check for vascular risk factors, mitochondrial disease, CADASIL, CAA, cerebral vasculitis	CADASIL is the only (rare) genetic disorder, all other cases are "sporadic"
FTLD 12%	bvFTD is the most heritable and SD the least heritable	Microtubule-associated protein tau (MAPT), progranulin (GRN) gene mutations
DLB 7%	Dementia is increasingly recognized as a common feature of advancing PD, but develops less frequently and with a longer latency in patients with young-onset disease	α-Synuclein triplications and mutations in the glucocerebrosidase gene can be associated with prominent cognitive impairment resembling classic dementia with Lewy bodies Mutations in the parkin (PARK2) gene are not typically associated with dementia
Alcoholic dementia 10%	Clinical features of alcohol exposure	NA
Other 19%	Variable	Variable

Adapted from Rossor et al. 2010. For abbreviations, see list at beginning of chapter

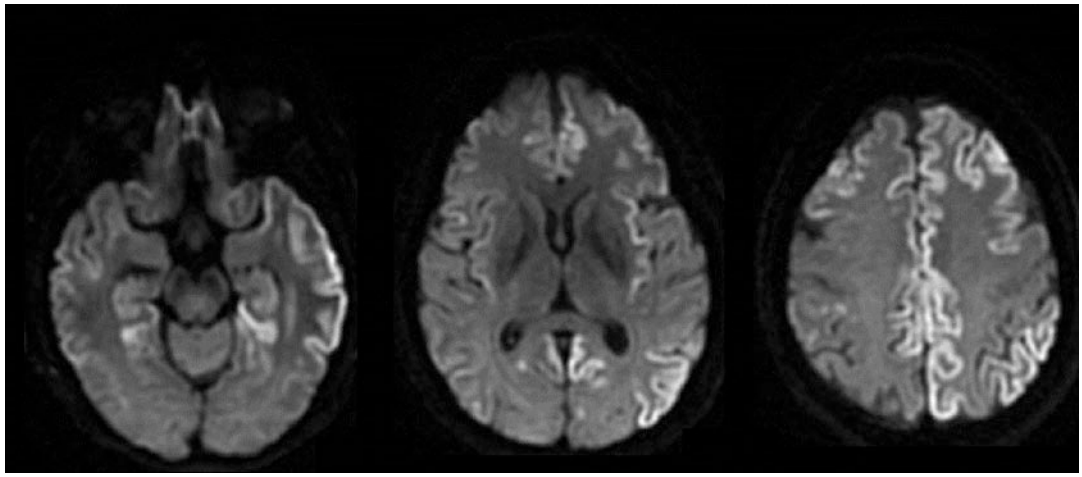

Fig. 3 DWI images show multifocal regions of cortical hyperintensities in a patient with CJD. Other CJD patients may have a striatal pattern. Both patterns are pathognomonic for CJD

notably CJD as the most common type of prion disease. CJD is caused by a cascade of abnormal protein folding and is mostly sporadic, though familial forms also exist. CJD variant (also known as mad cow disease, or Bovine spongiform) encephalopathy attracted attention in the general public in the 1990s, but due to various preventive measures, this disease is almost extinct today. In sporadic CJD typical imaging finding includes restricted diffusion on MRI in either neo-cortical regions (mostly multifocal) or in the striatum (usually symmetric) (Fig. 3). In familial fatal insomnia, the thalami are involved.

Corticobasal Syndrome (CBS)

The clinical picture of corticobasal syndrome (CBS) can be caused by CBD but also by other diseases, notably AD, PSP, and DLB. In most CBD cases, the presentation is with basal ganglia involvement (e.g., "alien-hand" syndrome) and will be discussed in detail in ▶ Chap. 49, "Neuroimaging in Movement Disorders." As the name suggests, there is also cortical involvement, and dementia (with aphasia and apraxia) may occasionally be the leading symptom (Rohrer 2012).

Table 3 Typical patterns of atrophy in dementia

Pattern of atrophy	Typical for	Also occurs in
Hippocampal atrophy	AD, esp. late-onset	FTLD (asymmetric), DLB (late)
Precuneus/parietal atrophy	PCA: Young-onset AD, DLB	CBS
Frontal atrophy	bvFTD	SD, PNFA, frontal type AD
Temporal pole atrophy	Semantic dementia	
Asymmetric hemispheric atrophy	CBD	Atypical AD
Mesencephalic atrophy (humming-bird)	PSP	VaD, MSA
Pontine atrophy (cross sign)	MSA	VaD, SCA

For abbreviations, see list at beginning of chapter

Patterns of Atrophy and Hypometabolism

Progressive atrophy on MRI or CT and hypometabolism on FDG PET are imaging hallmarks of neurodegeneration in dementia. The spatial patterns of atrophy and hypometabolism are more or less characteristic for the different types of dementia (Table 3), though there is a certain degree of overlap.

For example, predominantly parietal atrophy is associated with early-onset AD, but the differential diagnosis of PCA otherwise includes CBD and DLB. All these entities are associated with cognitive decline. The presence of associated basal ganglia atrophy may point towards CBD. Abnormality of the nigrosome 1 may point towards DLB, yet probably also towards CBD as a form of atypical parkinsonism.

Table 4 of ▶ Chap. 46, "Neurodegenerative Disorders: Classification and Imaging Strategy" summarizes the main metabolic abnormalities of the different neurodegenerative diseases associated with dementia and movement disorders.

Finally, molecular imaging can contribute to the differential diagnosis, usually in a multistep/exclusionary procedure.

DAT imaging, if normal, excludes the presence of nigro-striatal degeneration (in DLB, CBD, PSP, MSA).

Amyloid PET imaging may reveal a diffuse cortical uptake (no regional specificity as for atrophy). This may already occur in preclinical stages of AD and an abnormal scan hence has a positive predictive value. If amyloid PET is negative, however, it definitely excludes AD (high negative predictive value).

For tau-PET, the spatial patterns are more similar to atrophy patterns with early involvement of (medial) temporal lobes close to disease onset.

Most Prominent Dementing Diseases

Alzheimer Disease

Alzheimer dementia (AD) is by far the most common type of dementia, accounting for approximately 50–70% of dementia cases, even in young-onset cases, where FTD is relatively more common.

Typical AD (Memory Predominant AD)

Clinical Presentation

Typical senile AD is by far the most common type of AD and characterized by slowly progressive neurocognitive impairment. Short-term memory, i.e., the ability to remember recent events, is the first symptom in most cases. As the disease progresses, multiple additional symptoms may appear including language impairment, disorientation, mood disbalance, loss of motivation and self-care, and inappropriate behavior (oftentimes aggressive behavior towards relatives in the absence of other witnesses).

Pathomechanism

AD belongs to the group of taupathies and is characterized by extra-cellular amyloid plaques and intracellular neurofibrillary tangles. The exact pathomechanism of AD remains unclear despite extensive research. The currently mostly accepted theory is the so-called amyloid cascade hypothesis with extra-cellular amyloid plaques inducing intracellular tau, yet this cascade is probably not the unique pathway to AD. Possibly multiple pathways exist that may eventually lead to AD type dementia (Winblad et al. 2016).

The most well-established genetic risk factor for AD is the Apolipoprotein E (APOE) polymorphism. APO E3 is the most common type of allele occurring in around 79% of the normal population. APO E4 occurs in approximately 14% of people and is associated with increased risk of AD and atherosclerosis, while APO E2 in approximately 7% of people might have a small protective effect on AD. Abnormal imaging findings related with APO E4 status (e.g., mild hippocampal atrophy) are very subtle, and detectably only using advanced analysis techniques on a group level, yet not on visual analysis of individual patients. An increasing number of other genetic factors are being identified. The genetic risk of AD associated with those other genetic factors is in general not yet well established and rather modest. Dominant mutations such as in the APP or presenilin gene are found only in 1–2% of AD patients, typically those with a familial occurrence and young age-of-onset.

Imaging Findings (Table 4)

The most prominent imaging feature of typical AD is (disproportionate or not) hippocampal atrophy (Fig. 4). Several cut-off values for MTA have been proposed. We recommend the cut-off

Table 4 Key imaging findings in typical AD

MRI	FDG PET or ASL	AMYLOID PET	TAU PET
Hippocampal atrophy (patient <75 years: Mean MTA score ≥ 1.5 (average of both hemispheres) is abnormal. Patients >75 years: ≥2.0 is abnormal[a])	Hypometabolism/ hypoperfusion in PCC	Demonstrates abnormal accumulation in Amyloid in cortical distribution, may be present years before onset of symptoms	Abnormal tau accumulation, usually closer related to symptom onset
Usually to a lesser degree bilateral parietal atrophy	Occipital lobe normally spared	"Rule-in"	"Rule-out"
CMBs in lobar/mixed distribution			
White matter hyperintensities quite common (Fazekas 1 or 2)			

[a]Cut-off values as proposed by Pereira et al. (2014).

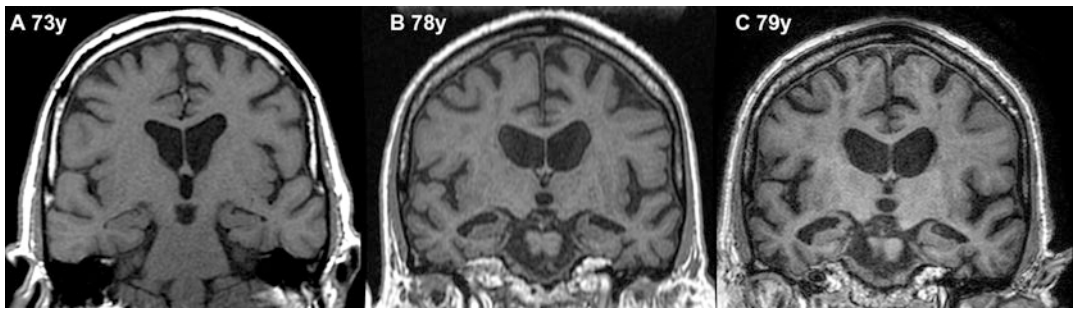

Fig. 4 Progressive hippocampal volume loss on coronal T1w images between age 73 (**a**, MTA 0), 78 (**b**, MTA 2), and 79 (**c**, MTA3) paralleled by progressive cognitive decline

proposed by Pereira et al. (Pereira et al. 2014). In general, in patient <75 years, an MTA score ≥ 1.5 based on the mean MTA scores of both hemispheres is abnormal (e.g., a score 2 on one side and 1 on the other side). Above 75 years of age, a cut-off of ≥2.0 is abnormal (e.g., a score 2 on both sides). Other supported features include parietal/precuneus atrophy (Koedam score 2 or more), more often found in isolation in AD cases with presenile-onset. Oftentimes, there is an overlap between AD and VaD, as many risk factors are overlapping. Consequently, a certain degree of white matter hyperintensities (WMH) exists on T2/FLAIR is often seen in AD. Moreover, there may be associated CMBs in a lobar distribution (though most cases will have none), and there is current debate regarding partial overlap in amyloid deposition in AD and CAA (discussed below).

Multiple software tools exist that quantify the degree of – notably hippocampal – atrophy. As discussed above, there is a large inter-individual variability in normal hippocampal volume, and hippocampal atrophy is also a feature of FTLD. Morphometry tools assessing the entire pattern of atrophy, notably the AD signature regions, while being more specific, are currently typically restricted to research setting only.

CSF Findings

More important than blood, analysis of cerebrospinal fluid (CSF) provides important information for the diagnosis of AD. The most established CSF markers are increased total tau (T-tau), increased phosphorylated tau (P-tau), and decreased β-amyloid notably Aβ42. In order to increase the sensitivity and specificity of the CSF markers, the combination (signature) of CSF Aβ42 and T-tau may detect mild AD and predict the conversion of MCI to AD (Trojanowski et al. 2010). However, none of those CSF markers is fully specific for AD, impeding the distinction with other dementias, such as DLB.

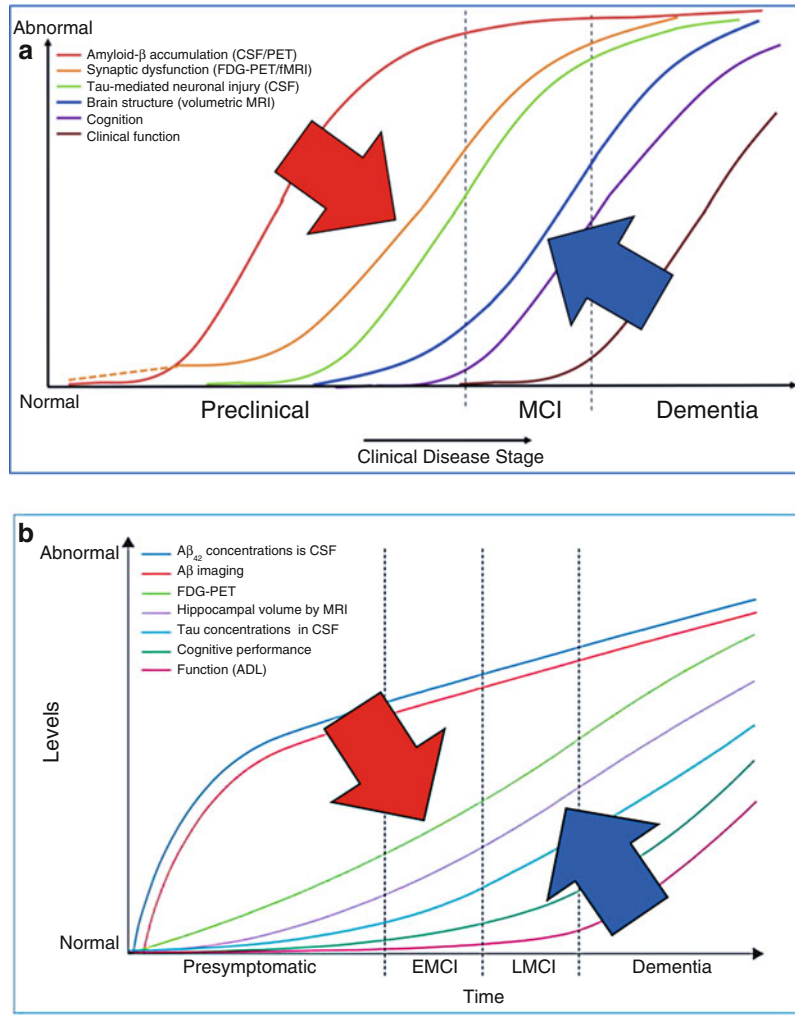

Fig. 5 Hypothetical models for the disease progression of AD. Despite differences between those models, there is agreement that functional changes, e.g., FDG PET (red arrow), precede structural changes, e.g., hippocampal atrophy (blue arrow). (Reprint with permission (**a**) Jack et al. 2010, (**b**) Petersen 2010)

Cascade of Progression of Neurodegeneration in MCI (Figs. 5 and 6, Table 5)

Mild cognitive impairment (MCI) is oftentimes considered as precursor state of progressive neurodegeneration and subsequent AD. It is however important to realize that MCI is a heterogeneous condition, and the definition of MCI continues to evolve. In an unselected group of patients with MCI, only about half of individuals will progress to AD in the next couple of years, while other cases may remain stable or even improve over time, and others may evolve to a different type of dementia. This makes early intervention or treatment trials for AD evidently difficult. Consequently, several subclassifications of MCI have been proposed, including, for example, amnestic MCI, frontal MCI, or multidomain MCI. Amnestic MCI cases have the highest likelihood to progress into AD at a later stage and are therefore of particular interest for early intervention or treatment trials.

Specificity of Imaging Findings and Preclinical AD

As discussed in ▶ Chap. 46, "Neurodegenerative Disorders: Classification and Imaging Strategy," there is a substantial interindividual variability in normal anatomy, disease resilience and cognitive reserve. Moreover, there is an overlap in clinical presentation and neurodegenerative diseases and the possibility of co-existence of, e.g., AD type

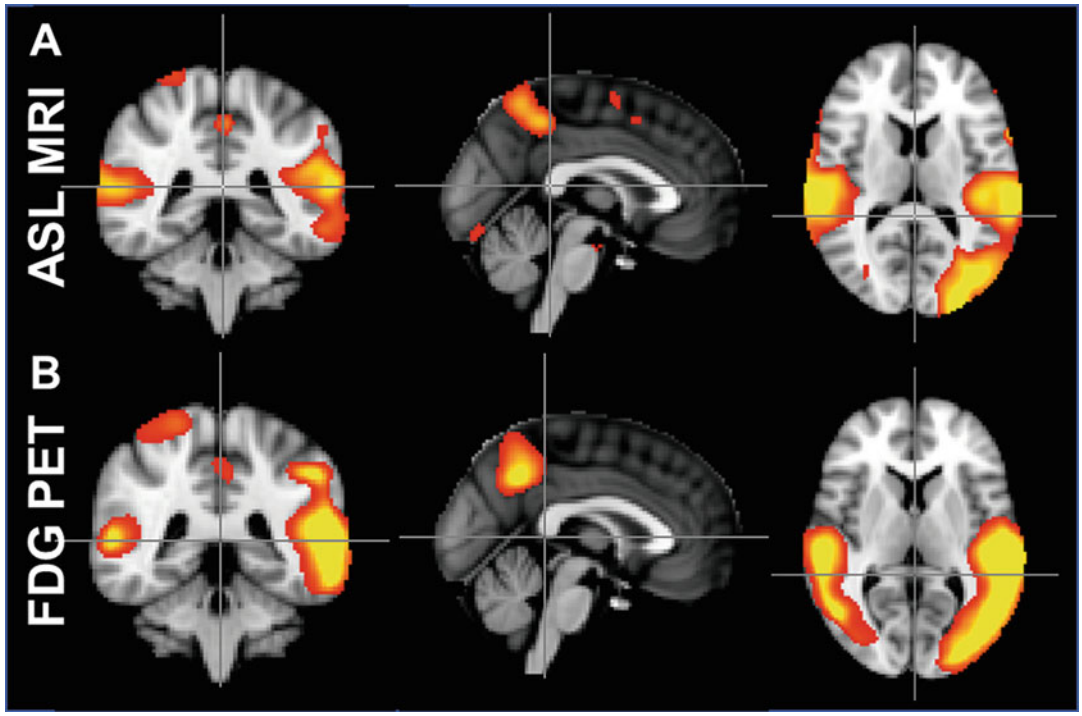

Fig. 6 Hypoperfusion map on ASL MRI (**a**) closely resembles hypometabolism on FDG PET (**b**) in a patient with AD

Table 5 Cascade of abnormal findings in AD

Amyloid PET	May be abnormal up to 10 years before onset of clinical symptoms
Tau PET	Abnormality more closely linked to onset of clinical symptoms
Functional abnormality: FDG PET/ASL MRI	Functional abnormality in prodromal (MCI) or early stages of AD
Structural abnormality: CT/MRI, notably incl. Hippocampal atrophy	Structural abnormality in general later than functional, visually evident structural abnormality in mild stages of AD

neurodegeneration and vascular pathology. As a consequence, there is no direct and linear correlation between imaging findings, e.g., hippocampal atrophy, and clinical symptoms of cognitive decline.

The recently coined term "suspected non-Alzheimer pathology" (SNAP) describes cognitively normal elderly individuals who have one or several markers of neurodegeneration (including hippocampal atrophy, abnormal FDG PET) but negative brain amyloid (Amyloid PET or CSF amyloid) and have not been diagnosed with a specific neurodegenerative disorder (Jack et al. 2012). It is currently believed that up to 25% of elderly persons with no or only subtle cognitive decline might fall into the category of SNAP. That means for the radiologist that the presence of e.g., hippocampal atrophy alone does not allow making the diagnosis of AD type dementia. Only those individuals with a combination of hippocampal atrophy, evidence of amyloid abnormality (PET or CSF), and subtle cognitive decline have an increased likelihood of progression to AD in the near future.

Variants of AD

Early-Onset or Young-onset AD

Clinical Presentation

If AD is diagnosed before the age of 65, it is oftentimes referred to as early-onset or young-onset

AD, accounting for 5–10% of all cases, outnumbering FTD in absolute terms in this age stratum. In addition to the younger age of onset, the clinical manifestation of juvenile AD is oftentimes more PCA-type and with less memory loss as compared to typical AD.

Pathomechanism

Approximately 10–15% of these cases, i.e., 0.5 – 1.3% of all AD cases, are familial AD. The currently established genetic factors of familial AD are mutations in Presenilin 1 or 2 (located on chromosomes 14 and 1, respectively) or Amyloid beta (A4) precursor protein (APP). Though younger cases are more likely to be familial, the yield of genetic testing remains very low.

Imaging Findings

In many cases of early onset AD (regardless whether familial or not), the atrophy pattern is more pronounced in the bilateral parietal region (Fig. 7), with less pronounced hippocampal atrophy – in contrast to the typical late-onset AD.

Behavioral Presentation of AD, Dysexecutive Presentation of AD Combined Behavioral/Dysexecutive Presentation of AD

There are several variants of AD, notably behavioral presentation, dysexecutive presentation, or combined behavioral/dysexecutive presentation of AD. The underlying pathology is AD type neurodegeneration. Although these variants are rare, it is important to be aware of these AD variants as it might sometimes explain apparently discrepant findings between clinical presentation and imaging finding. For example, a patient might present dominantly behavioral dysfunction which might suggest FTLD on clinical assessment, while imaging findings are more suggestive of AD (Fig. 8). This scenario could actually be a rare behavioral presentation AD, explaining the more FTLD like clinical presentation despite the more AD like imaging findings.

Clinical Presentation and Pathomechanism

The key clinical manifestation is evident in the naming of behavioral presentation, dysexecutive presentation, or combined behavioral/dysexecutive presentation of AD. The underlying pathology is equivalent to typical memory-predominant AD, yet the spatial distribution of abnormality might differ from typical AD, with, e.g., unusually pronounced involvement of the frontal lobes in behavioral presentation AD.

Imaging Findings and Differential Diagnosis

There are no evident differences in CT or MR imaging findings between those AD variants and typical AD, notably regarding visual analysis of individual cases. Abnormal amyloid status findings (CSF or PET) and notably abnormal spatial

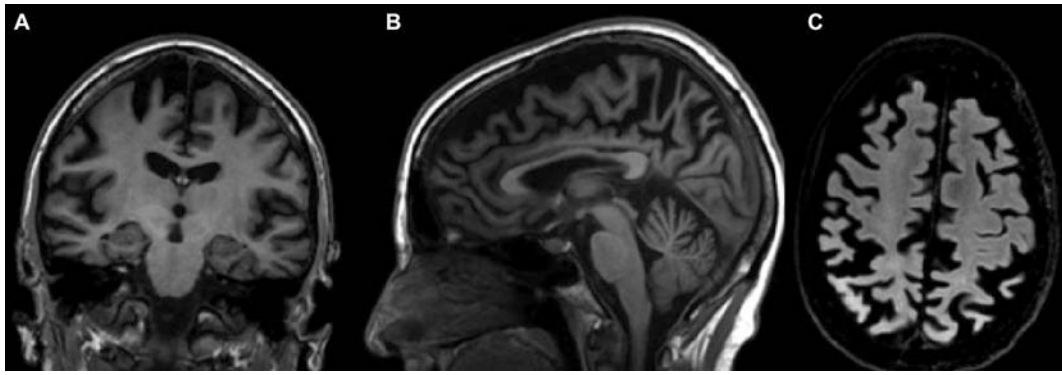

Fig. 7 Posterior cortical atrophy in young-onset case of AD (male, 57 years) with predominant visuospatial disturbances. Note the severe atrophy precuneus (sagittal) and the lateral parietal lobe (Koedam score 3), while the hippocampus is completely normal (MTA-score 0) on the coronal image. Coronal T1w (**a**), sagittal T1w (**b**), and axial T2 FLAIR (**c**)

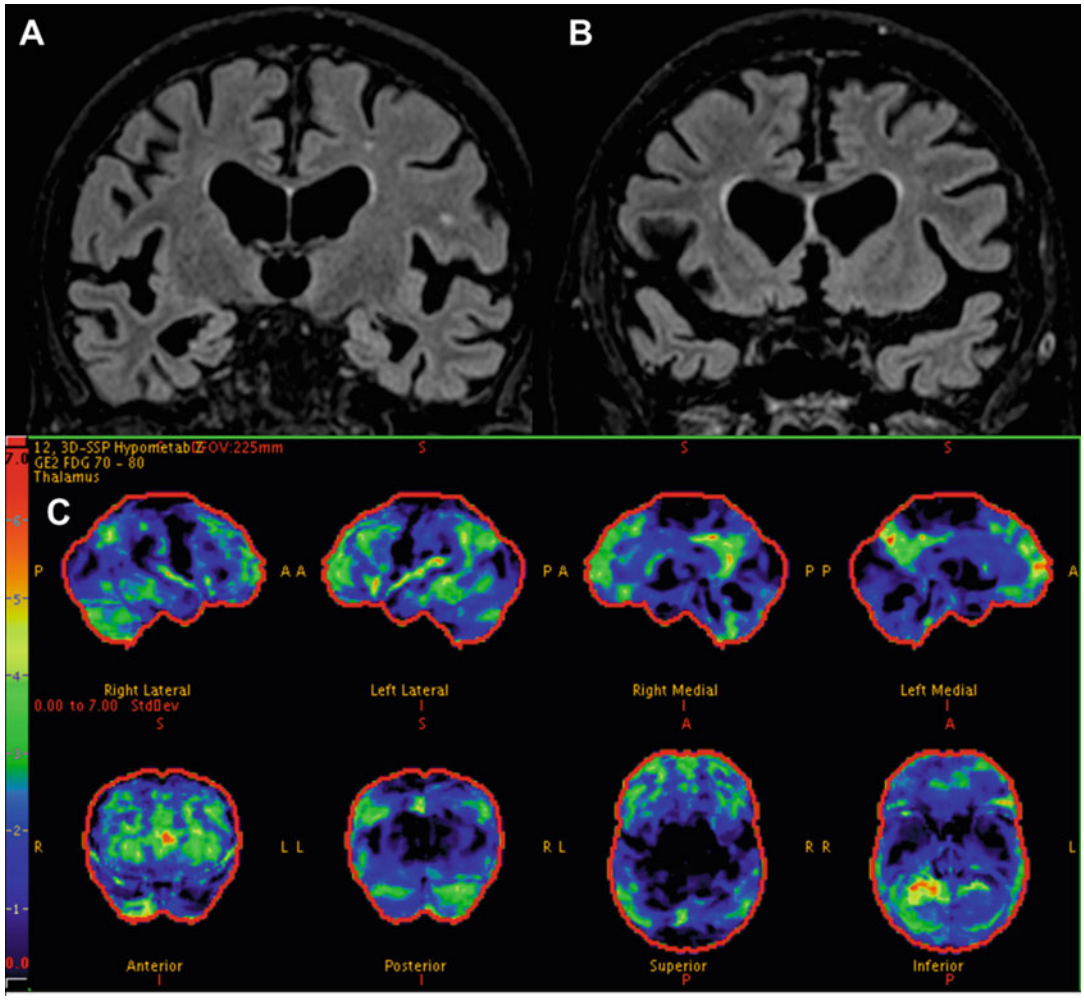

Fig. 8 Coronal reconstructed FLAIR (**a**) demonstrates significant hippocampal atrophy MTA 3 in a 78 years old man. To a lesser degree, there is associated frontal and anterior temporal atrophy (**b**). There is only minor white matter disease Fazekas 1. Parametric FDG PET (**c**) demonstrates hypometabolism notably in PCC sparing the occipital lobe and to a lesser degree frontal hypometabolism. The image is compatible with a frontal variant of AD, consistent with the clinical presentation of memory loss and associated frontal symptoms

distribution of tau PET might provide a diagnostic clue, yet this remains to be confirmed in future studies.

Logopenic Variant of PPA

Clinical Presentation and Pathomechanism

The logopenic variant of PPA, also referred to as "logopenic progressive aphasia" or "progressive mixed aphasia," is a rare variant of AD characterized by difficulties in word retrieval and consequently reduced speech rate. While this variant of PPA was traditionally considered as variant of FTLD due to the clinical manifestation (as discussed below), the underlying pathology is AD-type in the majority of cases.

Imaging Findings

Focal atrophy, affecting predominantly the left temporal lobe, is found in many cases notably on MRI and to a lesser degree in CT (Benamer et al. 2000). PET with tau tracers may demonstrate a more pronounced frontal involvement as compared to typical AD (Fig. 9).

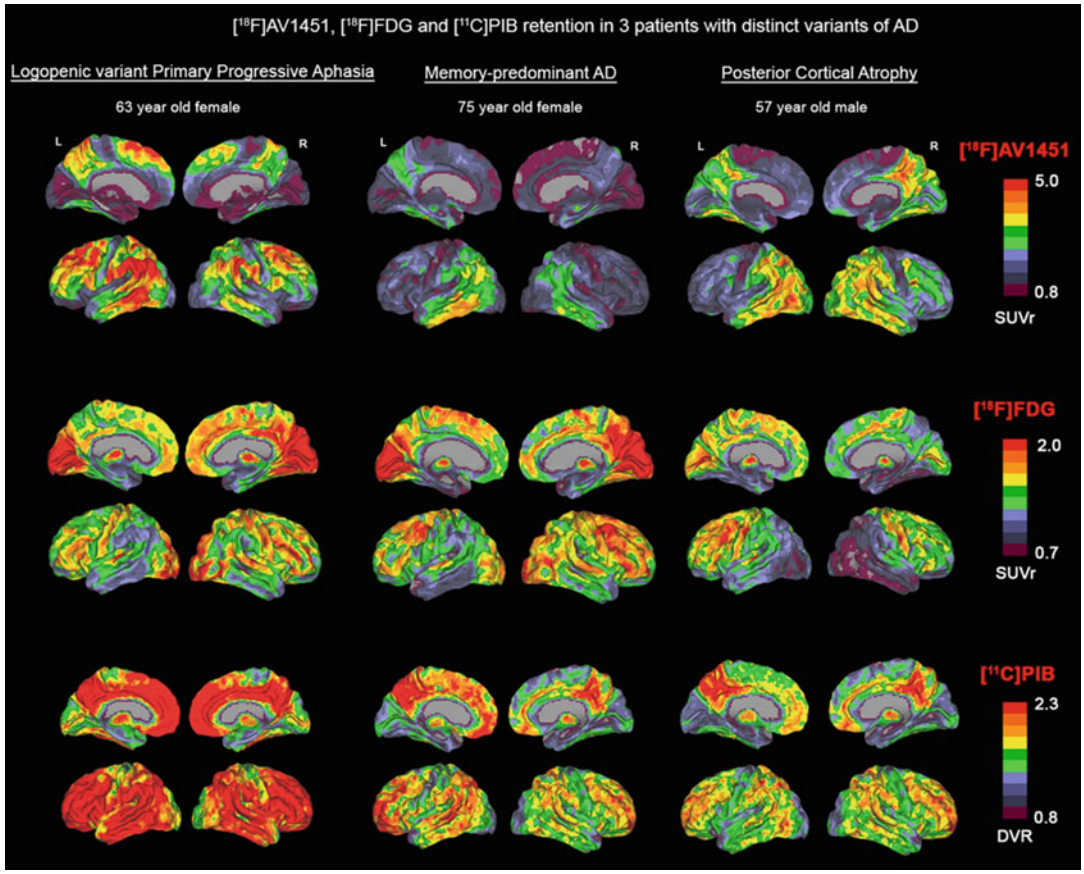

Fig. 9 Three cases with distinct variants of Alzheimer's disease show Tau PET (AV1451) uptake in distinct brain regions (top row). A woman with PPA (left) shows an intense signal in language areas while her frontal and occipital areas are spared; a woman with mild typical AD (middle) appears to have tau pathology in the inferior temporal cortex; a man with posterior cortical atrophy (right) shows the strong signal in occipital and tempoparietal regions. Glucose (FDG) PET revealed hypometabolic patterns predominantly in brain regions with high Tau PET (AV1451) uptake (middle row), although the spatial extent of glucose hypometabolism was less severe than that of tau pathology. Amyloid (PIB) PET (bottom row) indicated that the distribution of amyloid pathology was diffuse and symmetric, showing low regional specificity for neurodegenerative patterns and symptomatology. (Image courtesy of Rik Ossenkoppele and Gil Rabinovici)

Vascular Dementia

Clinical Presentation

Vascular dementia (VaD) is may occur as a completely separate disease, accounting for up to 20% of cases with dementia, and consequently the third largest group of dementia after AD and DLB. It is however increasingly recognized that oftentimes there is an overlap between a neurodegenerative disease, most commonly AD, and a vascular component (Fig. 10). In other words, having AD does not protect having vascular disease that is very common in the elderly, nor the inverse. It is further important to note that many risk factors such as hypertension, diabetes, etc., are overlapping between AD and VaD, and lifestyle modifications such as physical activity or Mediterranean diet may be beneficial for both AD and VaD. Importantly, it seems that a neurodegenerative (AD) component and vascular components might be supra-additive, meaning that an individual with mild AD type neurodegeneration

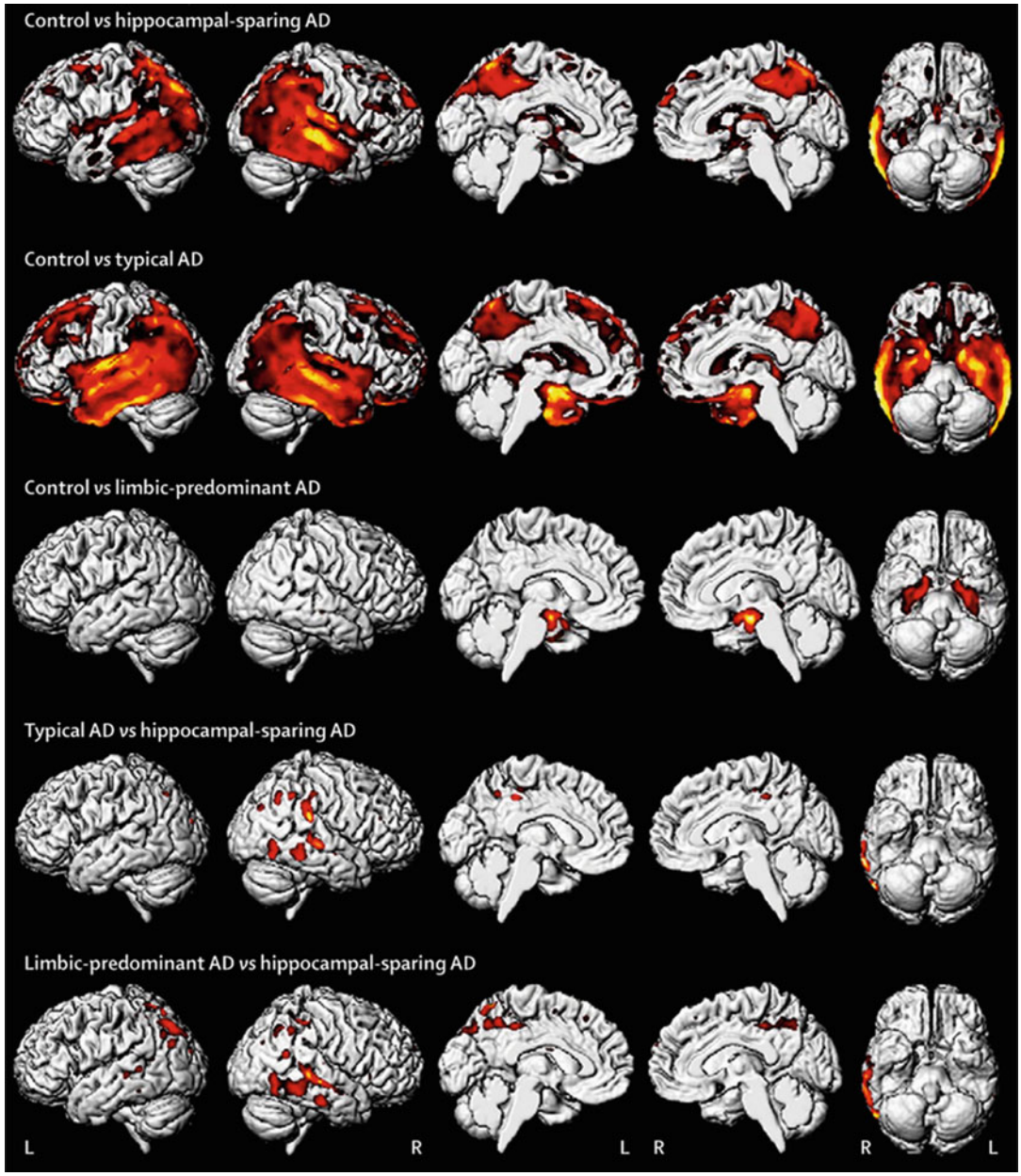

Fig. 10 Atrophy patterns in MRI in different variants of AD. Patients with hippocampal-sparing AD showed greater cortical loss than did those with typical and limbic-predominant AD, predominantly in the posterior temporal lobe, the inferior parietal lobe, and the precuneus; greatest loss was noted in the right hemisphere. Results are shown on three-dimensional renderings of the brain after correction for multiple comparisons, with family-wise error correction at $p < 0{\cdot}05$. Colors show T-score: yellow represents greater volume loss than red. AD = Alzheimer's disease. L = left hemisphere. R = right hemisphere. (Reprint with permission from Whitwell et al. 2012)

and mild microvascular brain disease may have neurocognitive decline that exceeds the simple addition of the neurodegenerative and vascular components (Haller and Barkhof 2017). Overall, this means that a certain degree of vascular compromise is very frequent in the elderly population that is at risk of developing neurocognitive decline. The true prevalence of a vascular

component is significantly higher than the approximately 20% of dementia cases in which vascular lesions are the only or at least leading cause of dementia.

Vascular dementia can be subdivided into small vessel disease (SVD) and large vessel disease (LVD).

Pathomechanism

There is a wide range of vascular risk factors including hypertension, diabetes, smoking, etc. Eventually those risk factors lead to atherosclerosis, hypercoagulation, and vascular lesions of different sizes. In principle, SVD and LVD have overlapping risk factors and pathomechanism, although in general lacunes are often due to small emboli, WMH due to arteriosclerosis (hypertension, diabetes) and LVD due to carotid disease.

Imaging Findings

Several criteria were proposed for the diagnosis of VaD, including the NINDS (National Institute of Neurological Disorders and Stroke)-AIREN (Association Internationale pour la Recherche et l'Enseignement en Neurosciences) criteria (Roman et al. 1993). The specific requirements for LVD and SVD findings to meet the NINDS-AIREN criteria are listed in Table 6 and comprise criteria for both topography and severity, to avoid making a false-positive diagnosis of VaD for example in cases with less marked vascular pathology (e.g., Fazekas 2 or infarcts in the non-dominant hemisphere) which could be an incidental finding in patients where the primary cause may be AD or another neurodegenerative disease.

These NINDS-AIREN criteria proposed in 1993 are however rather conservative and based on the assumption that VaD is a separate entity. As mentioned above, there is growing agreement that neurodegeneration and vascular pathology may co-exist, and the degree of vascular pathology may be variable. This assumption limits the use of such criteria that are based on the assumption of pure vascular-only pathology and implies the need for new and revised criteria for vascular pathology.

Table 6 Operational Definitions of the Imaging Guidelines of the NINDS-AIREN Criteria for VaD. (Reprint with permission from (van Straaten et al. 2003))

Topography
• Large-vessel infarcts – ACA – only bilateral ACA infarcts are sufficient to meet the NINDS-AIREN criteria – PCA – Infarcts in the PCA territory can be included only when they involve the following regions: • Paramedian thalamic infarction: the infarct extends into the paramedian part (defined as extending to the third ventricle) of the thalamus • Inferior medial temporal lobe lesions – Association areas – an MCA infarction needs to involve the following regions: • Parietotemporal: the infarct involves both the parietal and temporal lobe (e.g., angular gyrus) • Temporo-occipital: the infarct involves both the temporal and occipital lobe – Watershed carotid territories: an infarct in the watershed area between the MCA and PCA or the MCA and ACA involving the following regions: • Superior frontal region • Parietal region • Small-vessel disease – Ischemic pathology resulting from occlusion of small perforating arteries may manifest itself as lacunes or WMH. • Multiple basal ganglia and frontal white matter lacunes: at least 2 lacunes in the basal ganglia region (including thalamus and internal capsule) and at least 2 lacunes in the frontal white matter • Extensive WMH: confluent Fazekas grade 3 abnormality involving bilateral frontal and parietal lobes • Bilateral thalamic lesions: at least 1 lacune in each thalamus.
Severity
• Large-vessel disease of the dominant hemisphere – if there is a large-vessel infarct as defined above, to meet the criteria it has to be in the dominant hemisphere. In the absence of clinical information, the left hemisphere is considered dominant. • Bilateral large-vessel hemispheric strokes – 1 of the infarcts should involve an area listed under topography but is in the nondominant hemisphere, while the infarct in the dominant hemisphere does not meet the topography criteria. • WMH involving at least 1/4 of the total white matter – extensive white matter lesions are considered to involve 1/4 of the total white matter when they are confluent (Fazekas grade 3) in at least 2 regions (frontal/parietal) and beginning confluent (Fazekas grade 2) in 2 other regions.

ACA anterior cerebral artery, *PCA* posterior cerebral artery, *MCA* middle cerebral artery, *CSF* cerebrospinal fluid, *ARWMC* age-related white matter changes

Small Vessel Disease (SVD)

Small vessel disease (SVD) has three main components: microvascular leukoencephalopathy which can be assessed using the Fazekas score, lacunes, and cerebral microbleeds (CBMs). Those CMBs are generally in a central (thalamus and brainstem) distribution (rather than lobar as in AD or AA).

Lacunes, defined as CSF-like lesions between 3 and 15 mm, are often surrounded by peripheral gliosis with hyperintense signal on FLAIR, in contrast to enlarged VRS. In smaller lacunes, however, due to partial volume effects, the hypointense center on FLAIR might be less evident or absent, especially in the thalamus, where FLAIR tends to miss up to 50% of lesions (Fig. 11).

The spatial location of the T2/FLAIR hyperintensities affects the clinical implications of the lesions. In general, periventricular WMH might have less clinical relevance, because MRI tends to over-estimate those lesions with respect to the underlying gliosis, presumably due to the high concentration of local water contributing to the high local signal on T2/FLAIR (Haller et al. 2013b; Ylikoski et al. 1995; de Groot et al. 2000)

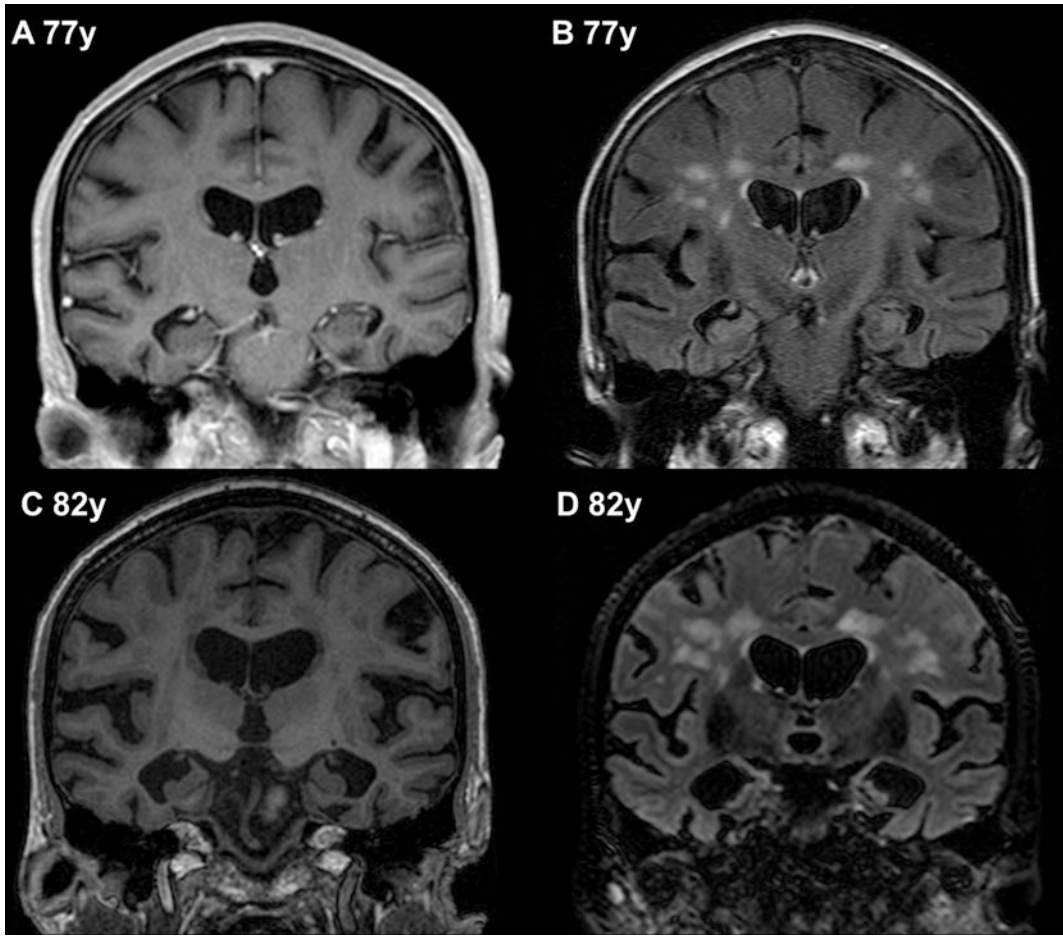

Fig. 11 Follow-up imaging of a case of mixed dementia of a woman with progressive cognitive decline. At age 77, there is mild to moderate hippocampal atrophy (**a**, coronal T1w MTA 1–2) and moderate microvascular leukoencephalopathy (**b**, coronal FLAIR, Fazekas 2). At follow-up imaging at age 82, both hippocampal atrophy (**c**, coronal T1w, MTA 3–4) and microvascular leukoencephalopathy (**d**, coronal FLAIR, Fazekas 3) are progressive

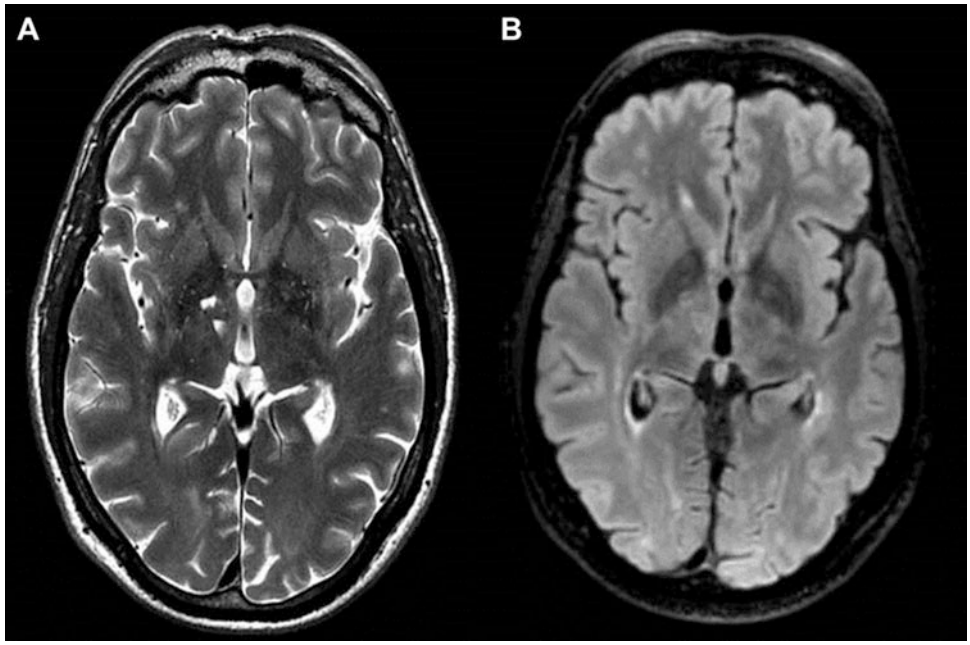

Fig. 12 Lacunes in right thalamus on axial T2w (**a**), barely visible on T2 FLAIR (**b**)

(Fig. 12). In contrast, deep WMH seem to have higher clinical importance and tend to be underestimated in MRI, presumably due to the lower local water concentration.

Concerning CMBs, their detection rate significantly depends on the MR technique (notably field strength and T2* versus SWI sequences), and MRI significantly underestimates the true rate of CMBs as compared to histopathology (Haller et al. 2018; Haller et al. 2016). Moreover, the clinico-radiologic correlation of those CMBs is very moderate (Barnaure et al. 2017). Finally, CMBs occur in increased frequency VaD, AD, and CAA, with a certain degree of overlap, as discussed in ▶ Chap. 49, "Neuroimaging in Movement Disorders."

Large Vessel Disease (LVD)

Vascular ischemic lesions ranging from lacunes to territorial infarcts (Fig. 13). For a detailed description of imaging findings see ▶ Chap. 6, "Major Artery Ischemic Stroke" STROKE. It is important to emphasize that not each vascular lesion meets the criteria for a VaD according to the NINDS – AIREN criteria (Table 6) (Fig. 14).

Cerebral Amyloid Angiopathy (CAA)

Cerebral amyloid angiopathy (CAA) is characterized by the deposition of β-amyloid in the media and adventitia of small and mid-sized arteries (and, less frequently, veins) of the cerebral cortex and the leptomeninges. Typical imaging findings include the presence of multiple microbleeds in lobar distribution, superficial hemosiderosis, leukoencephalopathy, and macroscopic lobar intraparenchymal hemorrhage, as discussed in detail in ▶ Chap. 9, "Imaging of Spontaneous Intracerebral Hemorrhage." CAA may lead to dementia in isolation, but also be part of the spectrum of AD. Consequently, there is a variable overlap between CAA and AD and finding hippocampal atrophy may help to distinguish (Fig. 15).

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant disease

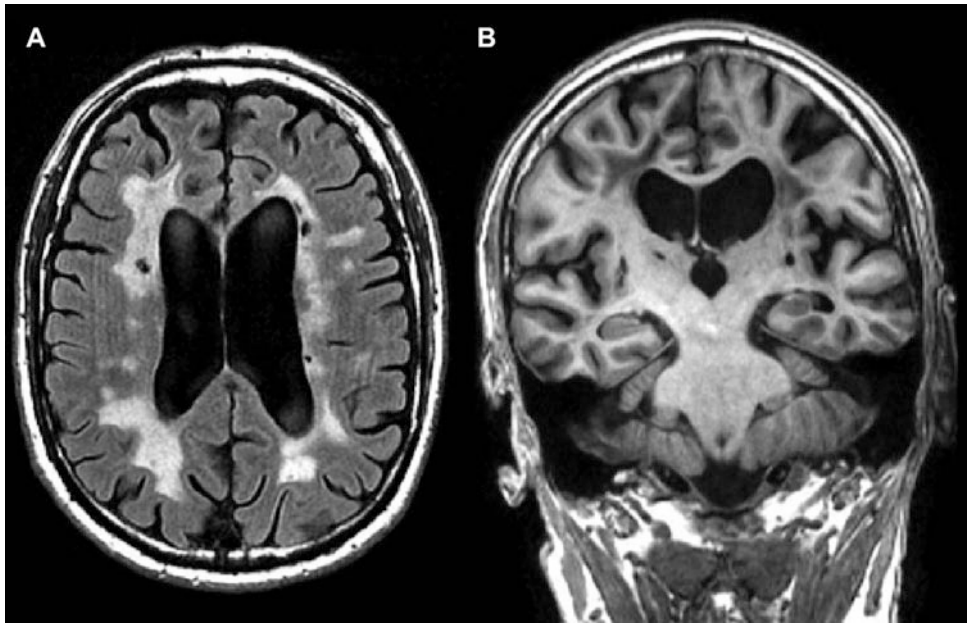

Fig. 13 Male 75-year-old dementia patient with confluent white matter hyperintensities (Fazekas 3) and multiple lacunes but perfectly preserved hippocampi (MTA score 0) consistent with pure VaD (small vessel disease subtype). More commonly patients with VaD also have some degree of hippocampal atrophy, consistent with mixed disease (VaD and AD). Axial T2 FLAIR (**a**) and coronal T1w (**b**)

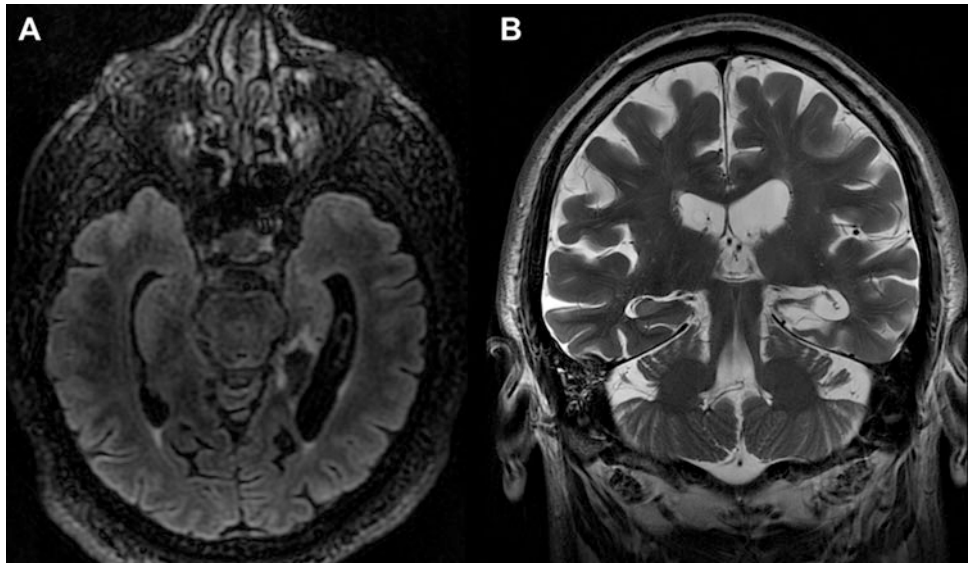

Fig. 14 80 years old patient with strategic stroke including the left corpus of hippocampus and para-hippocampal gyrus (**a**, axial FLAIR; **b** coronal T2w)

characterized by recurrent lacunar and subcortical white matter ischemic strokes, as discussed in detail in ►Chap. 7, "Small Vessel Disease." CADASIL may lead to vascular dementia in young and middle age patients without known vascular risk factors.

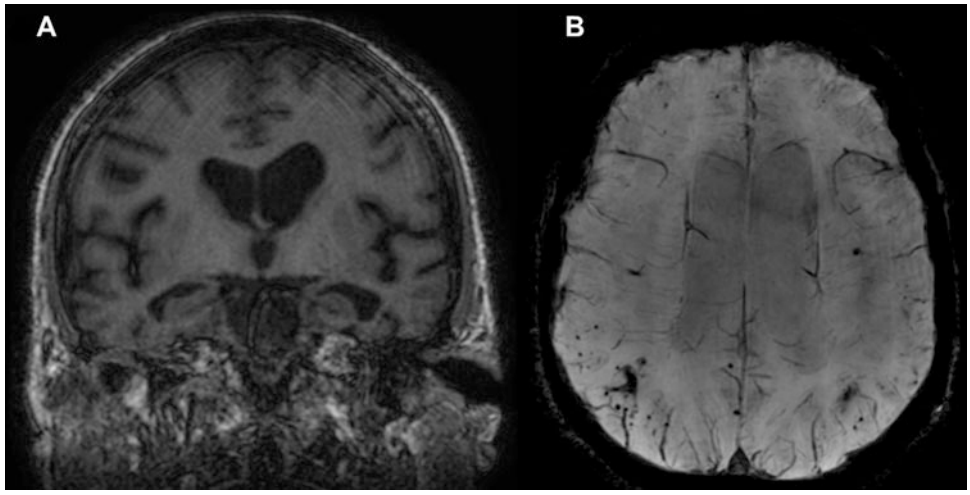

Fig. 15 Mixed pathology – CAA and AD. 69-year-old man with progressive memory loss. Coronal T1 (left) shows hippocampal atrophy (MTA 2 on right and MTA 3 on the left) suggestive of AD. Axial SWI (right) demonstrates multiples microbleeds in lobar distribution and superficial siderosis compatible with a probable CAA according to the revised Boston criteria. Coronal T1w (**a**), axial susceptibility imaging (**b**)

Dementia with Lewy Bodies (DLB)

Dementia with Lewy Bodies (DLB) is the second most common type of neurodegenerative dementia accounting for approximately 15–20% of cases, often before the age of 65. It may mimic AD clinically (and overlaps pathologically) and lacks specific MRI findings on standard sequences, hence difficult to diagnose.

Clinical Presentation

DLB is characterized by progressive memory loss, fluctuations in alertness, visual hallucinations, slowness of movement, troubles in walking, and rigidity. Additional symptoms may include excessive movement during (REM) sleep and mood changes such as depression. Differentiation from AD is important given adverse reaction to standard narcoleptics. CSF analysis is noninformative and no genetic abnormality can be detected.

Pathomechanism

DLB belongs to the group of synucleinopathies and is characterized by the abnormal accumulation of intracellular Lewy Bodies, i.e., eosinophilic protein aggregations. In addition, there often is a variable amount of Alzheimer-like pathological findings. DLB, Parkinson Disease (PD) and Parkinson Disease Dementia (PDD also known as PD+) are overlapping diseases. This explains why imaging findings in DLB and PD are overlapping, yet the clinical manifestation is different.

Imaging Findings (Table 7)

Standard MRI sequences show no reliable imaging findings in DLB (and PD), consequently DLB is underdiagnosed on standard MRI. Typically, there is little hippocampal atrophy (differentiating from AD) and some generalized atrophy including posterior regions (as in PCA). Nuclear medicine shows typical pattern of hypometabolism on FDG PET including the occipital lobe (while in contrast to AD sparing the posterior cingulate). Dopamine imaging (e.g., DaT scan) shows PD-type hypometabolism in striatum, resulting in a bilateral dot sing instead of a bilateral comma appearance, with excellent diagnostic accuracy (Fig. 16).

Recently, the swallow tail sing as an imaging marker of the nigrosome1 was introduced in the domain of PD (Schwarz et al. 2014). Due to the overlap in DLB/PD, this marker also works in DLB (Haller and Barkhof 2017), with diagnostic accuracy slightly below or in the range of dopamine imaging nuclear medicine (Kamagata et al. 2017; Shams et al. 2017) (Fig. 17).

Table 7 Key imaging findings in DLB

MRI	FDG PET	Dopamine nuclear medicine
Standard MRI: No specific findings Abnormal nigrosom1/swallow tail sign on SWI	Hypometabolism in bilateral parietal regions INCLUDING occipital lobe	Decreased dopamine uptake in striatum similar to PD: Bilateral dot sign instead of bilateral comma

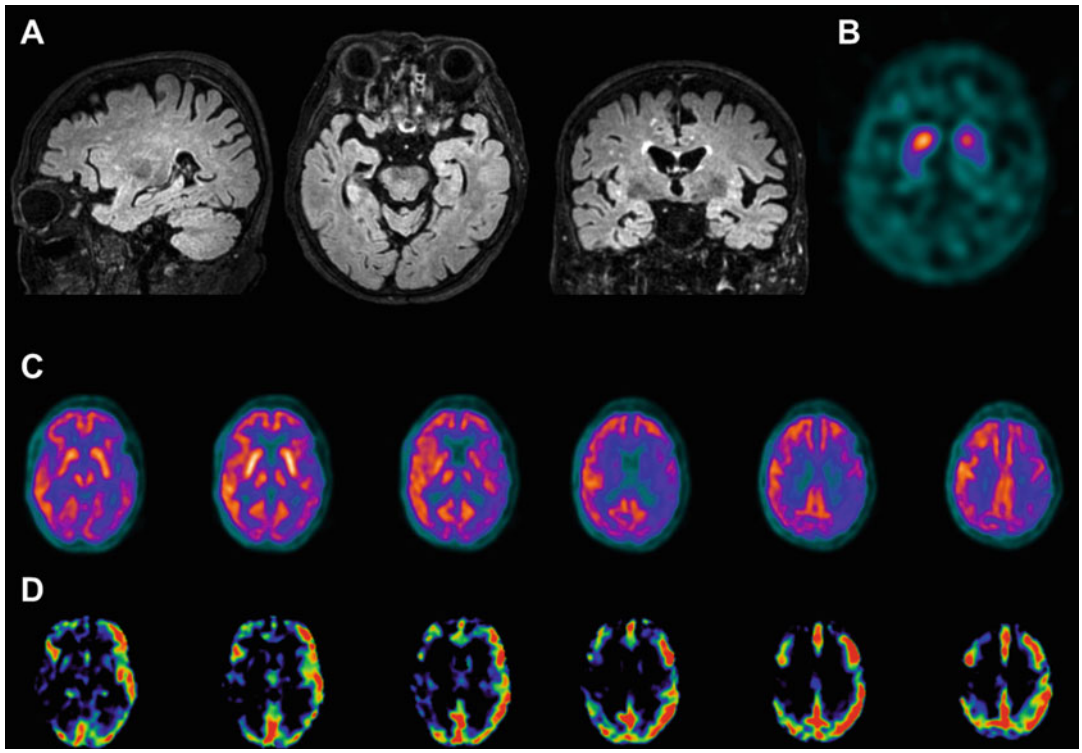

Fig. 16 Typical findings in dementia with Lewy bodies (DLB): nonspecific MRI findings (no prominent mesial temporal atrophy or vascular pathology – upper left), reduced DAT binding (upper right) and hypometabolism of the parieto-occipital cortex with relative sparing of the posterior cingulate cortex (middle row: normalized FDG PET images, lower row: comparison with a reference database, color-scale indicates standard deviation from normal values, ranging from 2 to 4)

Fronto-Temporal Lobar Degeneration (FTLD)

Fronto-temporal lobar degeneration (FTLD) is a heterogeneous group of dementing disorders characterized by behavioral and language problems, often with a young age-at-onset. Terminology and classification are sometimes contradictory and continuously changed over the last few years. The term fronto-temporal lobar degeneration (FTLD) is the pathological term, while fronto-temporal dementia (FTD) refers to the clinical symptoms of dementia. Subgroups include behavioral variant FTD (bvFTD), progressive nonfluent aphasia (PNFA), and semantic dementia (SD). CSF analysis may show increased tau (rather than phosphor-tau) and normal amyloid, in contrast to AD.

Pathomechanism

Most of FTLD subtypes, yet not all, belong to the group of taupathies, although some cases are due to ubiquitin pathology. Genetic testing may be abnormal in up to 20% of familial cases but is

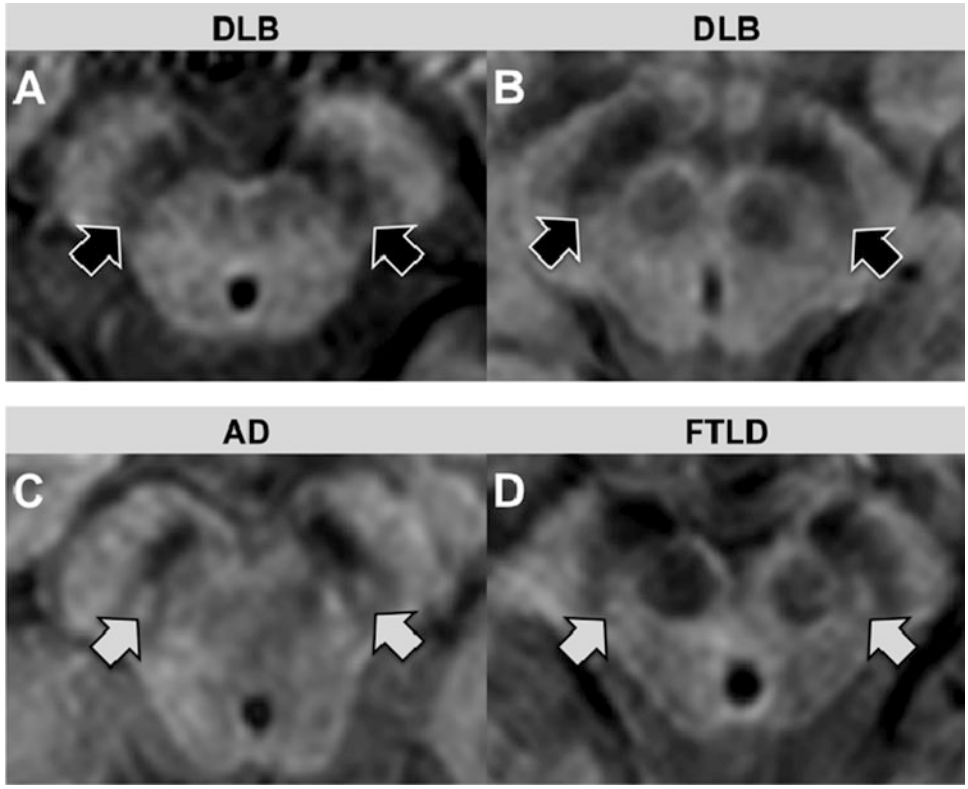

Fig. 17 Abnormal visualization of the nigrosome1 in two patients with DLB (top row) equivalent to the findings in PD. Normal visualization of the nigrosome1 in AD and FTLD patients (bottom row) (Haller et al. 2016)

less rewarding in sporadic cases. Mutations may involve the MAPT and progranulin gene, but also C9ORF, explaining (pathological) overlap with ALS and motor-neuron disease.

Imaging Findings (Table 8)

Although a detailed anatomical cortical measurement might reasonably well discriminate the main subtypes of FTLD (Lindberg et al. 2009), the imaging appearance of these forms of dementia bvFTD, PNFA, and SD are variable, with considerable overlap (Rohrer 2012). A radiologist should thus detect if the atrophy of a given patient has a focal predominance in the frontal and lateral-temporal regions with an anterior to posterior gradient to consider the differential diagnosis of FTLD without insisting on a specific subgroup diagnosis. SD cases tend to manifest with marked antero-temporal atrophy at the time of presentation, while bvFTD typically only have mild frontal atrophy at first presentation (Fig. 18).

Behavioral Variant of FTD (bvFTD)

Clinical Presentation

BvFTD (formerly also called Pick's disease) is characterized by changes in social behavior and conduct, with loss of social awareness and poor impulse control, leading to altered and often inappropriate behavior. Memory is usually relative unimpaired and language problems variable.

Imaging Findings (Fig. 19)

On MRI atrophy in frontal and anterior temporal lobes, with a characteristic anterior to posterior gradient, the mesio-frontal and orbito-frontal cortices are most early affected and there can be "ballooning" of the anterior horns of the lateral ventricles by local dilatation. Often there is some asymmetry and involvement of the temporal lobes as well. PET may show hypometabolism of the mesio-frontal and orbito-frontal gray matter.

Table 8 Key imaging findings FTLD

	Clinical presentation	MRI	FDG PET
Behavioral variant FTD (bvFTD)	Changes in social behavior and conduct, loss of social awareness and poor impulse control, inappropriate behavior. Memory is usually relative unimpaired, variable language problems	Atrophy in frontal and anterior temporal lobes, with a characteristic anterior to posterior gradient.	Hypometabolism frontal and anterior temporal lobes similar to pattern or atrophy
Semantic dementia (SD)	Loss of language understanding, impaired word comprehension, speech remains fluent and grammatically faultless.	Anterior temporo-polar atrophy more pronounced in left (dominant) hemisphere	Anterior temporo-polar hypometabolism
Progressive non-fluent aphasia (PNFA)	Progressive difficulties in speech production.	Bilateral peri-insular atrophy	Asymmetric left frontal and temporal hypometabolism
Right temporal variant of frontotemporal dementia	Disproportionate language dysfunction notably word-finding difficulties, prosopagnosia and increased obsessive personality/behavioral changes and comprehension problems	Similar to SD but on the right hemisphere	Similar to SD but on the right hemisphere

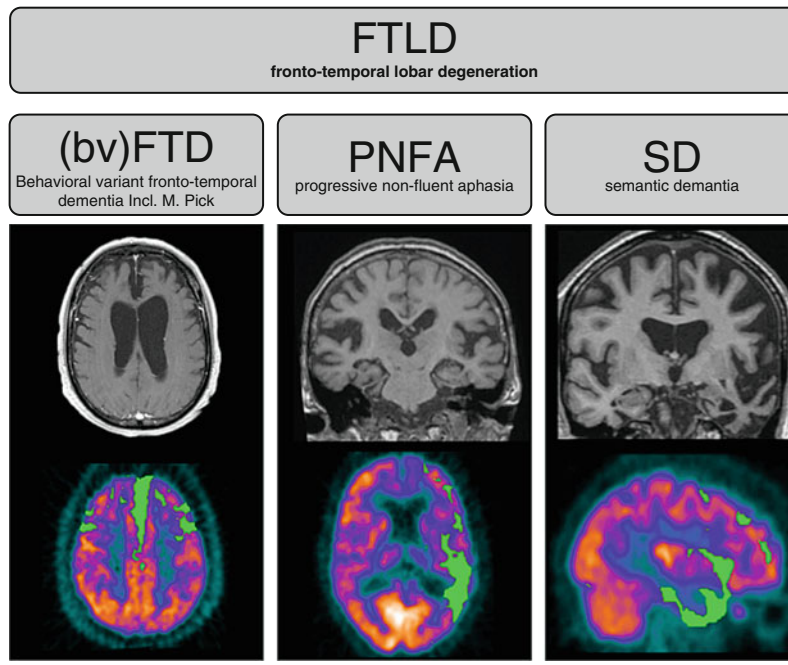

Fig. 18 Patterns of atrophy, and patterns of hypometabolism on FDG PET for the various subtypes of FTLD. (Reprint with permission from (Haller et al. 2013a))

Semantic Dementia (SD)

Clinical Presentation

Semantic dementia (SD) is characterized by the loss of language understanding, resulting in impaired word comprehension, although speech remains fluent and grammatically faultless.

Imaging Findings

On MRI usually severe anterior temporo-polar atrophy, more prominent on left (dominant) hemisphere. Often also marked hippocampal atrophy, strongly asymmetric to the left side with a posterior-anterior gradient. PET may show asymmetric hypometabolism of the temporal (and frontal) lobes.

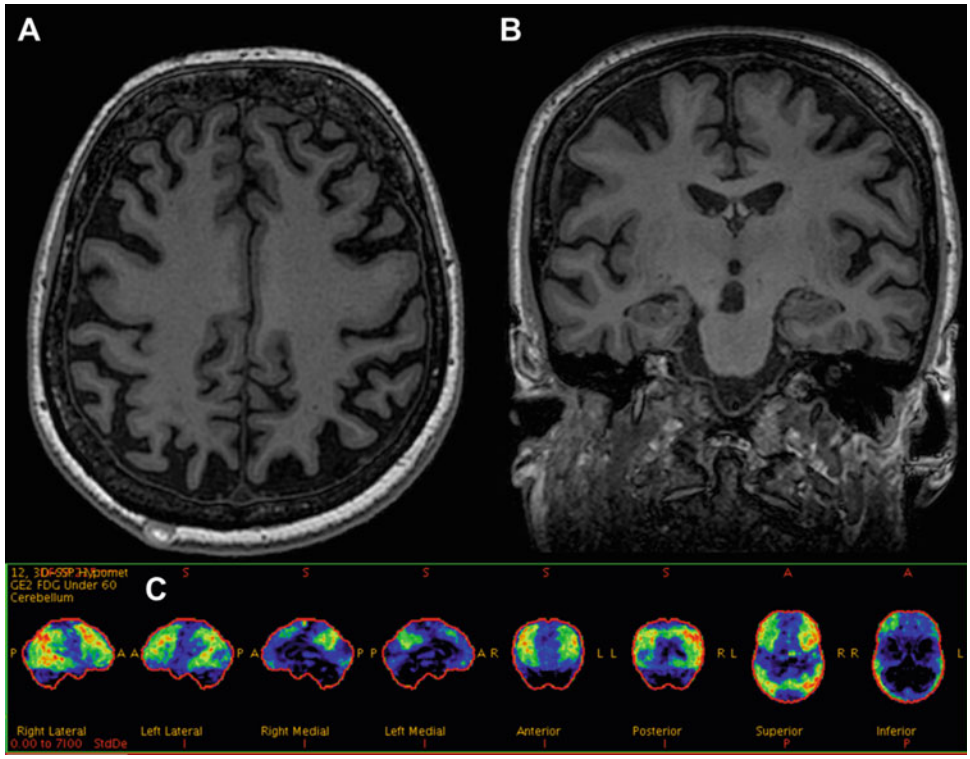

Fig. 19 52-year-old woman with progressive memory loss and frontal symptoms. Axial T1w MRI (**a**) demonstrates fronto-parietal atrophy, without significant hippocampal atrophy (MTA 0, **b**). Parametric analysis of FDG PET confirms hypometabolism in frontal, parietal, and temporal lobes sparing sensorimotor cortex and occipital lobe, consistent with bvFTD

Frontotemporal dementia (FTD) is a highly heritable condition with multiple genetic causes. Around 1/3 of cases are familial, most commonly related to mutations in 1 of 3 genes: Whole-brain voxel-wise analysis of GM demonstrates may detect subtle differences in atrophy patterns between those three common mutations (Fig. 20).

Progressive Nonfluent Aphasia (PNFA)

Clinical Presentation

PNFA is characterized by progressive difficulties in speech production.

Imaging Findings

MRI may show bilateral peri-insular atrophy, also affecting the inferior frontal gyrus (Broca's area) more marked on the left side. PET may show asymmetric hypometabolism of the frontal and temporal gray matter.

Right Temporal Variant of SD

Semantic dementia is characterized by left-hemispheric asymmetric temporo-polar atrophy. Most individual are right-handed, and the left hemisphere is dominant. It remains controversial whether the left-hemispheric predominant atrophy in SD is due to the fact that the left hemisphere is more heavily used and secondarily more atrophic. An alternative possibility is that as the left hemisphere is dominant in most individuals, atrophy-related functional loss of the left and dominant hemisphere is clinically more apparent and consequently lead to clinical diagnosis of symptoms of frontal dementia, while right-hemispheric atrophy and functional loss

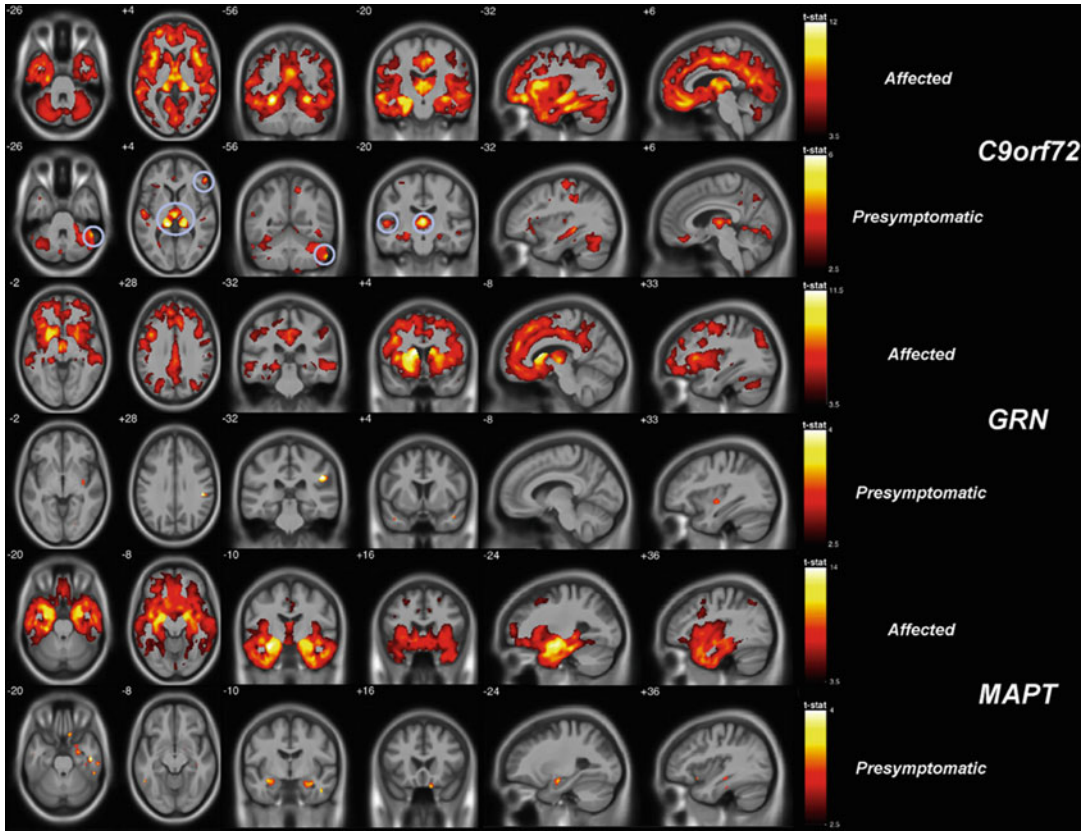

Fig. 20 Gray-matter (GM) differences for three common variants of familial FTD with mutations in chromosome 9 open reading frame 72 (C9orf72), progranulin (GRN), and microtubule-associated protein tau (MAPT). GM differences in affected (odd rows, $p < 0.05$ FWE-corrected) and presymptomatic (even rows, $p < 0.001$ uncorrected) carriers compared to noncarriers. Comparisons to the C9orf72 carriers are in the top 2 rows (with findings at $p < 0.05$, FWE-corrected circled in the presymptomatic group), the GRN carriers in the middle 2 rows, and MAPT carriers in the bottom 2 rows. (Reproduces with permission from Cash et al. 2018)

might be clinically less evident and consequently be under-diagnosed notably at early stages. In line with this latter hypothesis, the right-hemispheric analogue to SD or right-temporal variant of frontotemporal dementia attracts increasing attention in the last years, and the clinical symptomatology of this variant differs from typical left-hemispheric predominant SD and bvFTD including disproportionate language dysfunction notably word-finding difficulties, prosopagnosia, and increased obsessive personality/behavioral changes and comprehension problems (Kamminga et al. 2015; Josephs et al. 2009), presumably due to the specific engagement of both hemispheres in different cognitive domains (Fig. 21).

Overlapping Versus Distinct Neurodegenerative Diseases

As already discussed in ▶ Chap. 46, "Neurodegenerative Disorders: Classification and Imaging Strategy," the classic view is that the various neurodegenerative diseases are distinct entities. This is however not necessarily true. On the one hand there is overlap between different diseases, e.g., AD and CAA type microbleeds or AD and NPH. Finally, there is an overlap in the risk factors of, e.g., AD and vascular disease, and indeed the co-existence of several pathologies may interact and this may even be supra-additive (Haller and Barkhof 2017). Consequently, radiological

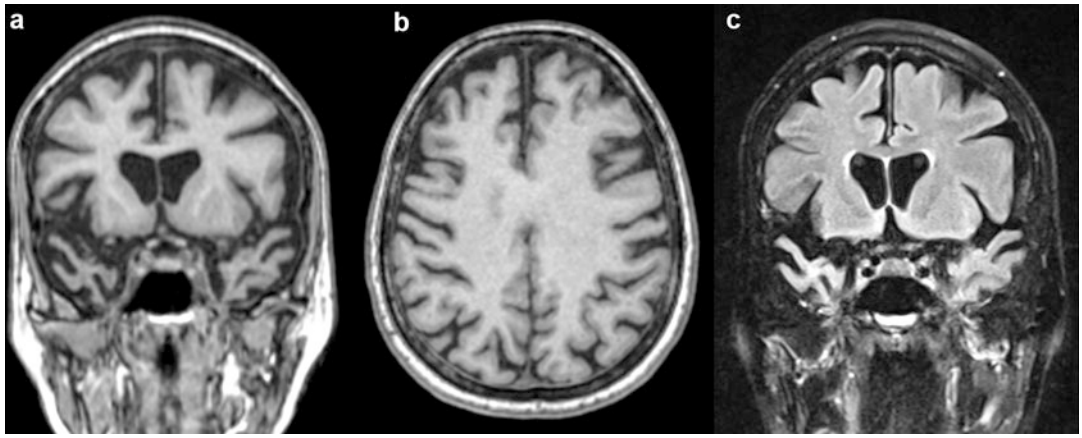

Fig. 21 62-year-old woman undergoing imaging for progressive neurocognitive impairment. Coronal T1 (**a**) demonstrates atrophy most pronounced on the temporal poles with anterior temporal atrophy score of 3 on the right and 2 on the left hemisphere. Axial T1 (**b**) shows only mild atrophy of the frontal lobes. Coronal T2w FLAIR (**c**) shows no significant associated vascular lesions and shows again atrophy most pronounced of the right temporal pole. In contrast to typical semantic dementia (SD) with atrophy pattern most pronounced in the left hemisphere, the current case is compatible with a right-temporal variant of SD

reporting should be probabilistic rather than deterministic and take into account the co-existence of, e.g., vascular and neurodegenerative changes (Figs. 19 and 22).

Overlap between Dementia and Movement Disorders

There is an overlap between dementia and movement disorders. DLB/PD/PDD are a spectrum of clinical presentations of abnormal intracellular accumulation of Lewy bodies. Imaging findings are similar, yet clinical presentation can be dominated by cognitive decline or extrapyramidal motor symptoms. Similarly, CBD, PSP, and MSA belong to the group of atypical parkinsonian syndromes and are in general characterized predominantly extrapyramidal motor symptoms; however, in some cases cognitive decline may be the dominant clinical manifestation, notably during early stages of the disease. Those movement disorder diseases will be discussed in detail in ► Chap. 49, "Neuroimaging in Movement Disorders."

Progressive Supranuclear Palsy (PSP)

Progressive supranuclear palsy (PSP) is primarily a neurodegenerative movement disorder characterized by a pattern of atrophy notably of the midbrain leading to the penguin or hummingbird sign. A subgroup of PSP patients develop neurocognitive decline also referred to as Steele-Richardson-Olszewski syndrome. FDG-PET images may show a typical cortical hypometabolism involving the whole prefrontal cortex, associated with hypometabolism in the basal ganglia, thalamus, and mesencephalon.

Corticobasal Syndrome (CBS)

Corticobasal syndrome (CBS) is, similar to PSP, primarily a neurodegenerative movement disorder with corticobasal degeneration, yet a subgroup of patients develops associated neurocognitive decline referred to as CBS. CBD typically has a bi-parietal focal atrophy. Unlike AD, bi-parietal focal atrophy is not associated with hippocampal atrophy but sometimes with infratentorial cerebellar atrophy. FDG-PET images typically show a unilateral or strongly asymmetric cortical (parietal, prefrontal, and motor cortex) and subcortical hypometabolism, contralateral to the affected body side.

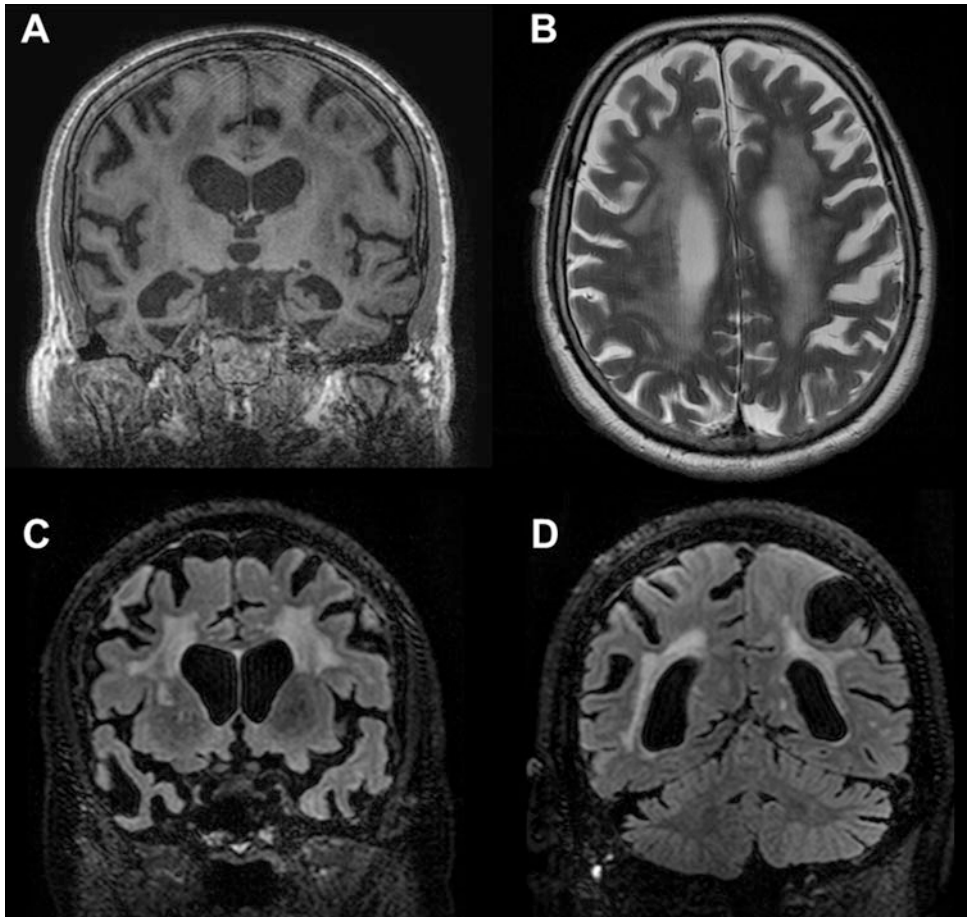

Fig. 22 88-year-old woman with progressive memory loss and loss of functional autonomy. Coronal T1w (**a**) demonstrates advanced hippocampal atrophy MTA 4 suggestive of AD type pathology. Axial T2w (**b**) demonstrates significant white matter disease Fazekas 3 suggestive of a vascular component. Coronal FLAIR (**c**, **d**) demonstrate atrophy of frontal, anterior temporal and parietal region including notably the right anterior temporal pole, suggestive of FTLD type pathology. In total, the imaging findings suggest a mixed type dementia

Neurodegeneration with Brain Iron Accumulation NBIA

Neurodegeneration with brain iron accumulation (NBIA) is a rare group of diseases characterized by brain iron accumulation notably in the basal ganglia, which will be discussed in detail in ▶ Chap. 49, "Neuroimaging in Movement Disorders." While NBIA in most cases is a disease of infants and children with extrapyramidal movement disorders, adult forms of NBIA exist and sometimes dementia may be the leading symptom.

Other Types of Dementias

The current chapter focused on neurodegenerative diseases and vascular diseases that may cause dementia. Evidently, the exclusion of a mass lesion is one of objectives of brain imaging. There are however multiple other diseases and conditions, which may cause cognitive decline and dementia. Most of those diseases and conditions are discussed in detail in other chapters. The most relevant other diseases and conditions in the context of dementia are briefly summarized below.

Psychiatric Diseases

Various types of psychiatric diseases may lead to a clinical symptomatology of cognitive decline and pseudo-dementia, despite the absence of a measurable neurodegenerative disease. Most commonly, such behavioral dementia-like symptoms are observed in depression and anxiety and may be confused with FTD. There are however no reliable imaging markers in standard CT or MRI related to those conditions.

Normal Pressure Hydrocephalus, NPH

Normal pressure hydrocephalus (NPH) remains a poorly understood disbalance between CSF production and CSF resorption resulting in the typical triad of cognitive decline, gait apraxia, and urinary incontinence. It belongs to the rare category of potentially treatable dementia, as subtractive CSF puncture or shunting may (partially) improve symptomatology, including cognitive status. Not only the underlying pathomechanism of NPH remains controversial, it also remains controversial whether there might be an overlap between AD and NPH. Similar to the overlap between AD and VaD discussed above, both conditions might co-exist in the same patient, and have additive or even supra-additive effects (see ▶ Chap. 18, "Communicating Hydrocephalus: Normal Pressure Hydrocephalus").

Various White and Grey Matter Diseases

There are numerous white and grey matter diseases which may be associated with dementia, including leukodystrophies, toxic, metabolic, infectious, or genetic origins. However, in general these diseases are rare causes of dementia. For example, progressive HIV-related encephalopathy (discussed in ▶ Chap. 25, "Infections in Immunocompromised Individuals") may be associated with progressive cognitive decline and dementia.

Therapy-Related Cognitive Impairment

Several types of therapy, notably radiation and chemotherapy in the context of malignancy, become more efficient and consequently patient survival increases. Consequently, the therapy-related side effects also become more pronounced and more frequent, including cognitive alterations related, e.g., to brain irradiation (both preventive and therapeutic) and chemotherapy. Imaging findings in this context are oftentimes unspecific and unremarkable, yet notably in the context of brain irradiation one might observe radiation-induced cerebral microbleeds and diffuse white-matter hyperintensity on FLAIR associated with chemotherapy.

Genetic Diseases

Some genetic diseases, for example, Trisomy 21, may lead to early-onset AD type cognitive decline (Fig. 23). Assessment of dementia in those genetic diseases is an emerging field. Oftentimes, typical memory predominant cognitive impairment is a leading symptom, which may be

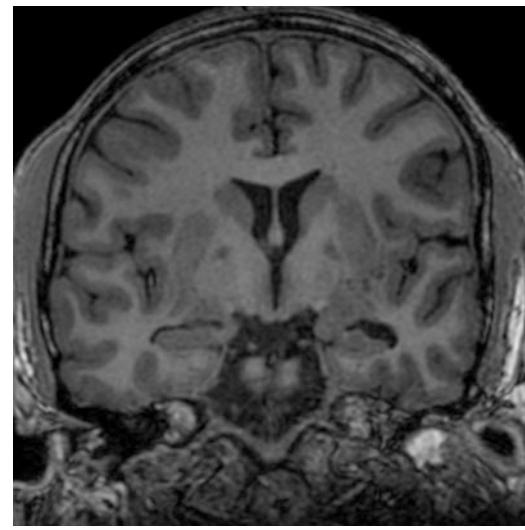

Fig. 23 Example case of a 35-year-old patient with Trisomy 21 and recent onset of memory loss. Note the mild hippocampal atrophy notably on the left hemisphere, with an MTA of 2 on left and MTA of 1 on right hemisphere. An MTA score of 2 is disproportional to the young age. Coronal T1w

associated with variable other behavioral or psychiatric anomalies (Fig. 23).

Leukodystrophies and Multiple Sclerosis

Leukodystrophies are a heterogeneous group of progressive white matter diseases, which often present in childhood, but occasionally may present well into adulthood. There is however growing recognition of leukodystrophies during adulthood, which may present with dementia, as discussed in ▶ Chap. 59, "Leukodystrophies and Inherited Metabolic Conditions." Disease to consider includes adrenomyeloneuropathy (mutations in ABCD1 gene), hereditary diffuse leukoencephalopathy with axonal spheroids (CSF1R mutations), mitochondrial disease (DARS2 mutations), and vanishing white matter disease (eIF2B mutations). Multiple sclerosis (MS), although often presenting with focal neurological complaints, may remain clinically silent and present first with dementia late in life. In more typical MS, there often is a marked neurodegenerative component, leading to cognitive impairment during the disease course.

Checklist for Reporting

See ▶ Chap. 46, "Neurodegenerative Disorders: Classification and Imaging Strategy."

Sample Reports

Sample Report Dementia Negative

MRI Brain:
Technique
Recording according to the dementia protocol.
Description
No previous imaging of the brain available for comparison.
Supra-tentorial
No significant or focal atrophy, normal volume of the hippocampi (MTA 0 both sides). No significant focal vascular white matter lesions (Fazekas 0). No lacunar infarcts or microbleeds. No diffusion restriction. Normal gray-white differentiation. No mass effect.
Infra-tentorial
No focal lesion or focal atrophy. Normal visualization of the nigrosome 1
Optional: ASL
Symmetric perfusion at rest, no focal hypo- or hyper-perfusion
Additional findings
Beginning arthrosis of the cranio-cervical junction
Conclusion
Absence of significant neurodegenerative or vascular abnormalities can be demonstrated that can provide an explanation for the memory complaints (Fig. 24).

Sample Report Dementia Positive

MRI Brain:
Technique
Recording according to the dementia protocol.
Description
No previous imaging of the brain available for comparison.
Supra-tentorial
Moderate to advanced atrophy, most pronounced of the hippocampi (MTA 2 on right and MTA 3 on left hemisphere). Mild small focal vascular white matter lesions (Fazekas 1). No lacunar infarcts or microbleeds. No diffusion restriction. Normal gray-white differentiation. No mass effect.
Infra-tentorial
No focal lesion or focal atrophy. Normal visualization of the nigrosome 1
Optional: ASL
Slight hypoperfusion in the posterior cingulate cortex and bilateral parietal region.
Additional findings
None
Conclusion
Moderate to advanced atrophy notably of the hippocampus suggestive of moderate neurodegeneration of AD type, without a significant vascular component (Fig. 25).

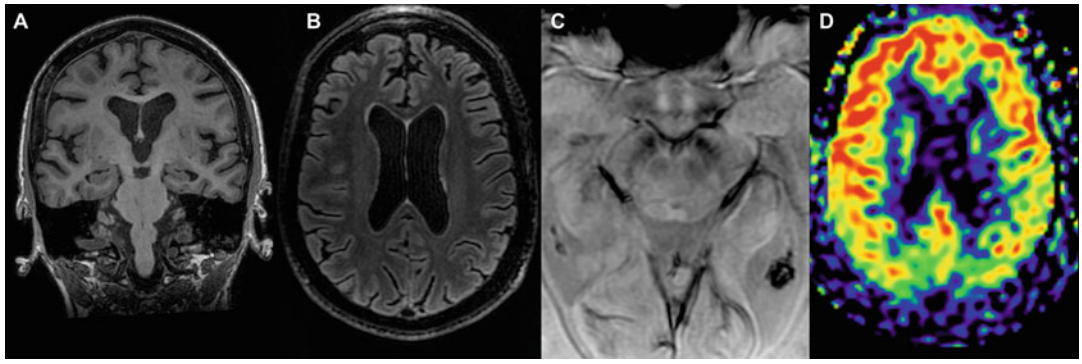

Fig. 24 Normal report of a 72-year-old woman. Para-coronal (along the axis of the temporal lobe) reformatted T1w (**a**), axial reformatted 3D T2w FLAIR (**b**), zoom of axial susceptibility imaging (**c**), and axial ASL (**d**)

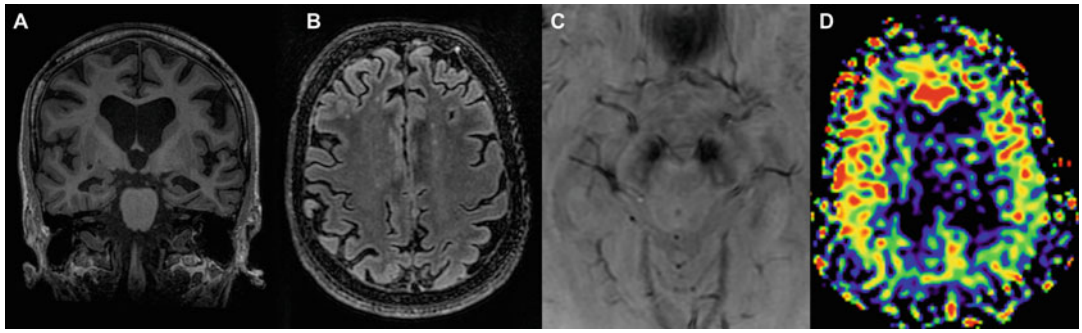

Fig. 25 76-year-old woman with moderate AD symptomatology. Para-coronal (along the axis of the temporal lobe) reformatted T1w (**a**), axial reformatted 3D T2w FLAIR (**b**), zoom of axial susceptibility imaging (**c**), and axial ASL (**d**)

References

Benamer TS, Patterson J, Grosset DG, et al. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group. Mov Disord. 2000;15:503–10.

Haller S, Vernooij MW, Kuijer JPA, et al. Cerebral microbleeds: imaging and clinical significance. Radiology. 2018;287:11–28.

Lindberg O, Ostberg P, Zandbelt BB, et al. Cortical morphometric subclassification of frontotemporal lobar degeneration. AJNR Am J Neuroradiol. 2009;30:1233–9.

Paterson RW, Takada LT, Geschwind MD. Diagnosis and treatment of rapidly progressive dementias. Neurol Clin Pract. 2012;2:187–200.

Petersen RC. Alzheimer's disease: progress in prediction. Lancet Neurol. 2010;9:4–5.

Trojanowski JQ, Vandeerstichele H, Korecka M, et al. Update on the biomarker core of the Alzheimer's disease Neuroimaging Initiative subjects. Alzheimers Dement. 2010;6:230–8.

Winblad B, Amouyel P, Andrieu S, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol. 2016;15:455–532.

Further Reading

Cash DM, Bocchetta M, Thomas DL, et al. Patterns of gray matter atrophy in genetic frontotemporal dementia: results from the GENFI study. Neurobiol Aging. 2018;62:191–6.

Haller S, Barkhof F. Interaction of vascular damage and Alzheimer dementia: focal damage and disconnection. Radiology. 2017;282:311–3.

Haller S, Garibotto V, Kövari E, et al. Neuroimaging of dementia in 2013: what radiologists need to know. Eur Radiol. 2013a;23:3393–404.

Haller S, Kövari E, Herrmann FR, et al. Do brain T2/FLAIR white matter hyperintensities correspond to myelin loss in normal aging? A radiologic-neuropathologic correlation study. Acta Neuropathol Commun. 2013b;1:14.

Haller S, Fällmar D, Larsson EM. Susceptibility weighted imaging in dementia with Lewy bodies: will it resolve the blind spot of MRI. Neuroradiology. 2016;58:217–8.
http://www.radiologyassistant.nl/en/p43dbf6d16f98d/dementia-role-of-mri.html
http://www.springer.com/de/book/9783642008177
Jack CRJ, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010;9:119–28.
Jack CR, Knopman DS, Weigand SD, et al. An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. Ann Neurol. 2012;71:765–75.
Josephs KA, Whitwell JL, Knopman DS, et al. Two distinct subtypes of right temporal variant frontotemporal dementia. Neurology. 2009;73:1443–50.
Kamminga J, Kumfor F, Burrell JR, Piguet O, Hodges JR, Irish M. Differentiating between right-lateralised semantic dementia and behavioural-variant frontotemporal dementia: an examination of clinical characteristics and emotion processing. J Neurol Neurosurg Psychiatry. 2015;86:1082–8.
Pereira JB, Cavallin L, Spulber G, et al. Influence of age, disease onset and ApoE4 on visual medial temporal lobe atrophy cut-offs. J Intern Med. 2014;275:317–30.
Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993;43:250–60.
Rohrer JD. Structural brain imaging in frontotemporal dementia. Biochim Biophys Acta. 2012;1822:325–32.
Rossor MN, Fox NC, Mummery CJ, Schott JM, Warren JD. The diagnosis of young-onset dementia. Lancet Neurol. 2010;9:793–806.
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:e93814.
van Straaten EC, Scheltens P, Knol DL, et al. Operational definitions for the NINDS-AIREN criteria for vascular dementia: an interobserver study. Stroke. 2003;34:1907–12.
Whitwell JL, Dickson DW, Murray ME, et al. Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study. Lancet Neurol. 2012;11:868–77.
Ylikoski A, Erkinjuntti T, Raininko R, Sarna S, Sulkava R, Tilvis R. White matter hyperintensities on MRI in the neurologically nondiseased elderly. Analysis of cohorts of consecutive subjects aged 55 to 85 years living at home. Stroke. 1995;26:1171–7.