Degenerative Diseases of the CNS

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14.1 Alzheimer's Disease (AD)

AD is the most prevalent dementia with its main risk factor being older age. By 2050, the number of people living with AD in the United States is projected to reach 13.8 million, resulting in nearly 1 million new cases per year [1]. Although the sporadic rather than the familial forms of the disease is by far the most prevalent, 20 genes with common variants contribute to the risk of AD [2]. In particular, the occurrence of ε4 genotype of the apolipoprotein E is the strongest genetic risk factor for AD [3]. The pathologic lesions of AD are neuritic plaques (NPs) around a core of beta amyloid (Aβ) and intracellular neurofibrillary tangles (NFTs) composed of aggregates of hyperphosphorylated microtubule-associated tau protein. The "amyloid hypothesis of AD" states that the imbalance between production and clearance of Aβ42 and related Aβ peptides is the determining, very early factor in AD [4]. NFTs lesions have a sequential pattern of deposition in the brain, appearing first in the entorhinal cortex, later in the hippocampal formation and finally in isocortical association areas, which has been used to stage the disease [5].

Clinically, AD patients have an insidious onset of cognitive decline heralded by episodic amnesia. Executive dysfunction, visuospatial difficulties, aphasia, apraxia, and agnosia develop subsequently and variably. Patients with cognitive impairment that do not meet diagnosis of dementia are labeled as mild cognitive impairment (MCI), whose prevalence is estimated between 15 and 20% for 60 years and older [6]. MCI patients progress to AD at a yearly rate of 10–15%, and predictors of this conversion include whether the patient is a carrier of the ε4 allele of the apolipoprotein E (APOE) gene, clinical severity, brain atrophy on imaging, positive CSF biomarkers, cerebral glucose metabolism, and Aβ deposition [7]. Revised criteria for the diagnosis of AD recommend biomarkers derived from structural MRI, CSF analysis, and PET to complement clinical criteria with objective evidence of the underlying neuropathology [8].

The Alzheimer's Disease Neuroimaging Initiative (ADNI) led to the development of clinical, imaging, genetic, and biochemical biomarkers for the early detection and longitudinal assessment of control subjects, MCI, and AD patients [9]. The radiologic hallmark of AD is atrophy of mesial temporal structures, i.e., the hippocampus and parahippocampal gyrus, which is present at the MCI stage and progresses along with the disease [10] (Fig. 14.1). At the mild

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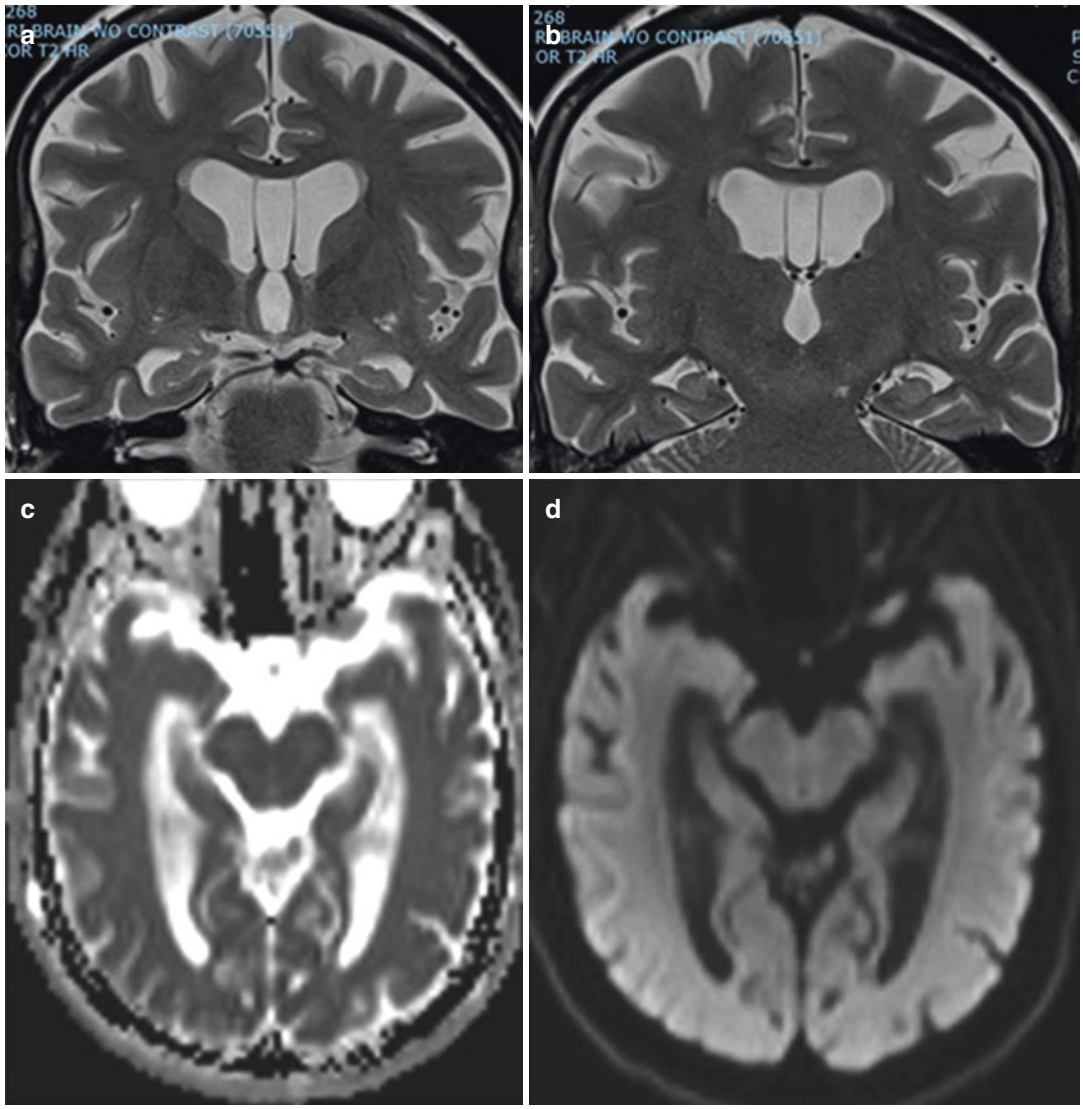


Fig. 14.1 66-year-old female with Alzheimer's dementia. (**a**, **b**) Coronal T2 with severe hippocampal atrophy. (**c**, **d**) Axial ADC map and trace DWI along the temporal horns

dementia stage of AD, hippocampal volume is reduced by 15–30% relative to controls, and in the amnestic variant of MCI hippocampal volume is reduced by 10–15% [10]. The topography of brain tissue loss correlates with cognitive deficits, both cross-sectionally and longitudinally, and recapitulates the Braak's pathology stages [5]. Apart from mesial temporal atrophy, whole-brain atrophy and ventricular enlargement predict underlying Aβ and tau pathology [11]. Furthermore, the annual rate of hippocampal volume loss distinguishes MCI patients that progress to dementia (accelerated atrophy) from those that remain stable (lower rate of atrophy) [12]. Apart from structural imaging, metabolic imaging biomarkers of AD are cortical hypometabolism and amyloid/tau accumulation on PET, the latter showing the earliest brain changes in AD [9].

The concept of AD being inevitable with advanced aging has been challenged since the neuropathology of dementia of the very old (over 95 years) shows stagnation in the incidence of AD while vascular dementia and hippocampal

sclerosis of aging (HS aging), a TDP 43 proteinopathy, become increasingly prevalent [13]. The co-occurrence of AD and vascular brain injury (VBI) in the elderly is very common and contributes to cognitive dysfunction in an additive and independent fashion. White matter T2 signal hyperintensities (leukoaraiosis [14]), lacunar or large infarcts and hemorrhages are visible on MRI and currently constitute the most reliable biomarker for VBI [15].

14.1.1 DWI in AD

DWI is typically not part of the clinical diagnosis of AD but contributed significant value to the understanding of brain pathology in AD, particularly white matter involvement, by using DTI. Hippocampal atrophy, the MRI hallmark of AD, is related to subsequent disruption of the uncinate fasciculus and the cingulum bundle in amnestic MCI as determined by DTI tractography analysis. Fiber loss in these white matter tracts is also related to metabolic decrease in the posterior cingulate and medial orbitofrontal cortices [16]. This degeneration seems to be closely related with, and is possibly a consequence of, medial temporal atrophy. Hippocampal ADC is higher in MCI and AD patients [17, 18]. ADC values in the hippocampal formation are elevated before conventional MRI reflects early changes in the progression of AD. ADC of the temporal stem and posterior cingulate, occipital, and parietal white matter is higher in AD compared to controls. Widespread changes in DTI metrics have been reported in bilateral limbic and association white matter tracts at the MCI and mild AD stages of the disease [19]. Increased mean, axial, and radial diffusivity occur in normal-appearing white matter of AD patients, with less significant reduction in fractional anisotropy, and these changes were correlated with gray matter atrophy. In MCI, axial diffusivity was increased in the limbic network and the cortico-cortical pathways, whereas the mean diffusivity, fractional anisotropy, and radial diffusivity values were preserved [20]. Studies of the ADNI cohort have found both global and local changes of WM tracts during AD progression with globally increased axial diffusivity and radial diffusivity in MCI patients, and further increase in these DTI measures, along with decreased global fractional anisotropy (FA) in demented subjects, consistent with widespread WM damage [21].

14.1.2 Atypical AD Variants

Clinical, radiological, and pathologically [22] atypical presentations of AD have been described, which tend to present in younger patients (under 65 years). These include the following:

- Posterior cortical atrophy (PCA) [23], presents with unusual visuoperceptual symptoms, such as diminished ability to interpret, locate, or reach for objects under visual guidance; visual agnosia and deficits in numeracy, literacy, and praxis. Episodic memory and insight are initially relatively preserved, but there is later progression to a more diffuse pattern of cognitive dysfunction. On imaging, there is predominantly posterior parietal cortical atrophy with relative preservation of the medial temporal lobe volume [24].
- Frontal variant AD, with prominent behavioral disturbances and apathy resembling FTLD and predominant frontal lobe atrophy [25].
- Language presentation with fluent or nonfluent aphasia and logopenic AD variant, with asymmetric left temporal lateral cortical atrophy [26].

14.1.3 Other Tauopathies

Hyperphosphorylated aggregates of the microtubule-associated protein tau are the main component of the intracellular inclusions seen in the neurodegenerative diseases known as tauopathies. These include AD, frontotemporal dementia with parkinsonism-17 (FTDP-17), Pick disease (PiD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) [27].

14.1.3.1 Corticobasal Degeneration (CBD)

CBD has varied clinical presentations. Typically presents with the corticobasal syndrome: asymmetric parkinsonism with a variable combination of ideomotor apraxia, rigidity, myoclonus, and dystonia, often associated with the presence of an alien limb phenomenon (involuntary motor activity of a limb with feeling of estrangement from that limb) [28]. On macroscopic exam and structural imaging, there is hemiatrophy or bilateral asymmetrical cortical atrophy, which predominates in the perirolandic or in the perisylvian areas (Fig. 14.2). The recent development of selective in vivo tau PET imaging ligands such as [(18)F]THK523 provides support for diagnosis of CBD and other tauopathies [29]. The characteristic microscopic hallmark of CBD is the swollen ballooned neuron and more specifically the astrocytic plaque, a non-amyloid cortical plaque composed of abnormal tau in the distal processes of astrocytes [30].

14.1.3.2 Progressive Supranuclear Palsy (PSP)

PSP presents most characteristically with a constellation of supranuclear gaze palsy (although seen only a minority of patients), progressive axial rigidity, pseudobulbar palsy, and dementia [31]. Tufted astrocytes filled with tau inclusions are the characteristic microscopic lesion [30]. On structural imaging and using simple measurements, the reduced area of the midbrain relative to the pons [32] or the enlarged third ventricle [33] allows distinction of PSP from controls and Parkinson's disease (PD) patients with high specificity (Fig. 14.3). The superior cerebellar peduncle (SCP) is also atrophic in PSP, which contrasts with the relative sparing of the middle cerebellar peduncle (MCP). These features were incorporated into the MR Parkinsonism index (MRPI), which takes into account both the midbrain-pons area ratio (P/M) and the ratio of the MCP to SCP width, thus: [(P/M)*(MCP/SCP)]. The MRPI is typically

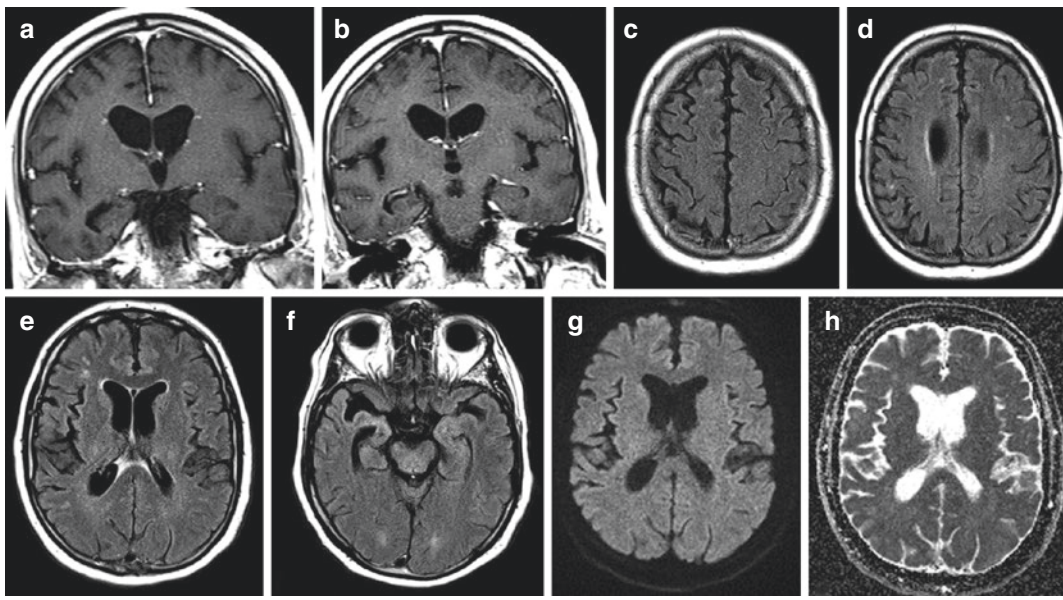


Fig. 14.2 CBD. 64-year-old patient with a history of dementia, left-sided weakness, numbness, dysarthria, mild dystonia, hyperreflexia, and apraxia worse on left side and involuntary alien limb movements. (**a, b**) Coronal T1, (**c-f**) Axial FLAIR, (**g**) trace DWI, and (**h**) ADC map. Asymmetric right cortical atrophy. **FDG PET of same CBD** patient (**i** axial, **j** coronal images) with right frontotemporal hypometabolism

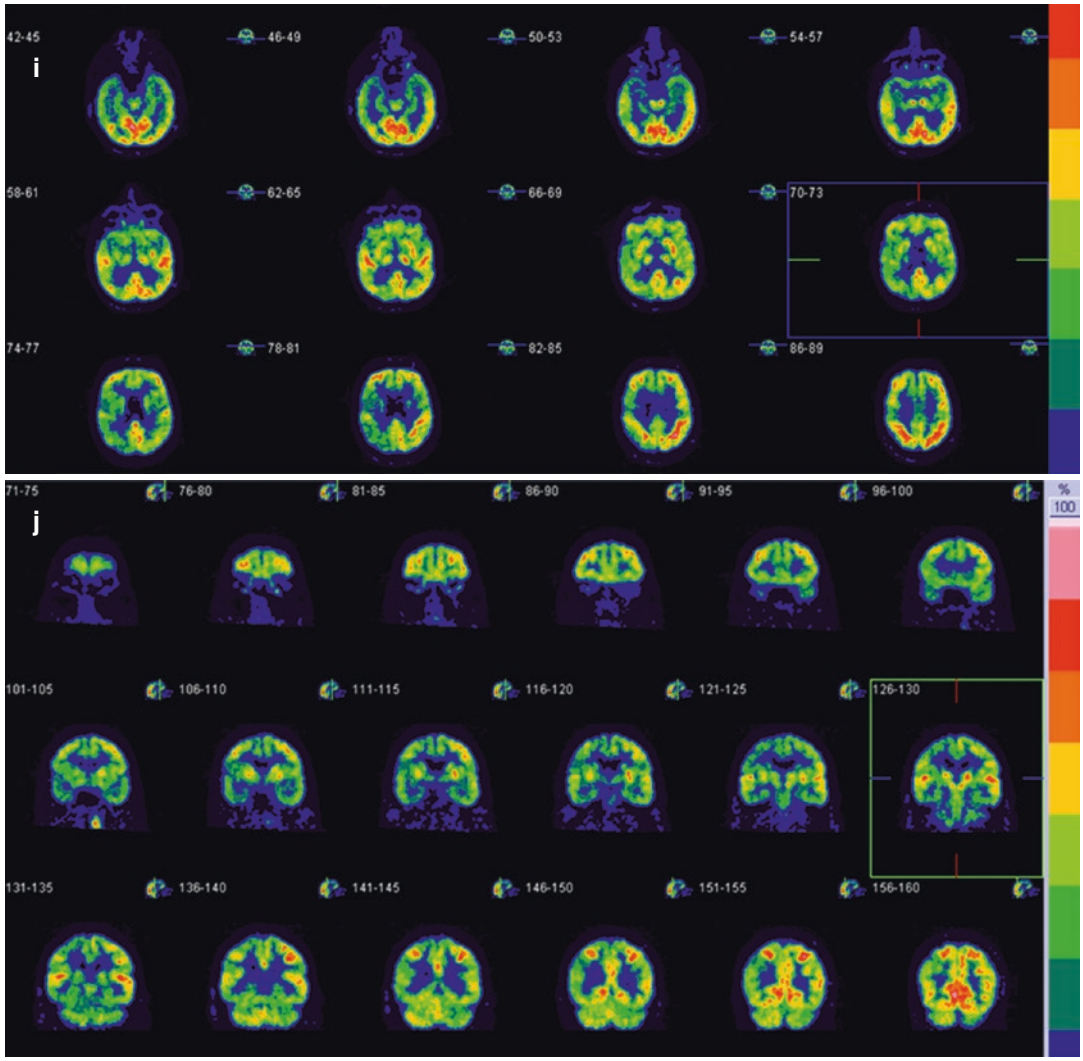


Fig. 14.2 (continued)

increased in PSP compared to controls, MSA-P and PD, and sensitivity and specificity values for the differential diagnosis of PSP from MSA-P, PD, and vascular parkinsonism have been reported between 80 and 100% [34]. Furthermore, a meta-analysis of studies with a total of 159 PSP patients showed significant white matter volume reductions compared to controls in the midbrain, pons, and the regions close to the basal ganglia [35].

14.2 Dementia with Lewy Body Disease (LBD)

LBD is the second most prevalent degenerative dementia after AD. The essential clinical feature of LBD is dementia, with prominent deficits in attention, executive function, and visuospatial skills. The revised LBD consensus criteria distinguish clearly between clinical features and diagnostic biomarkers, including neuroimaging

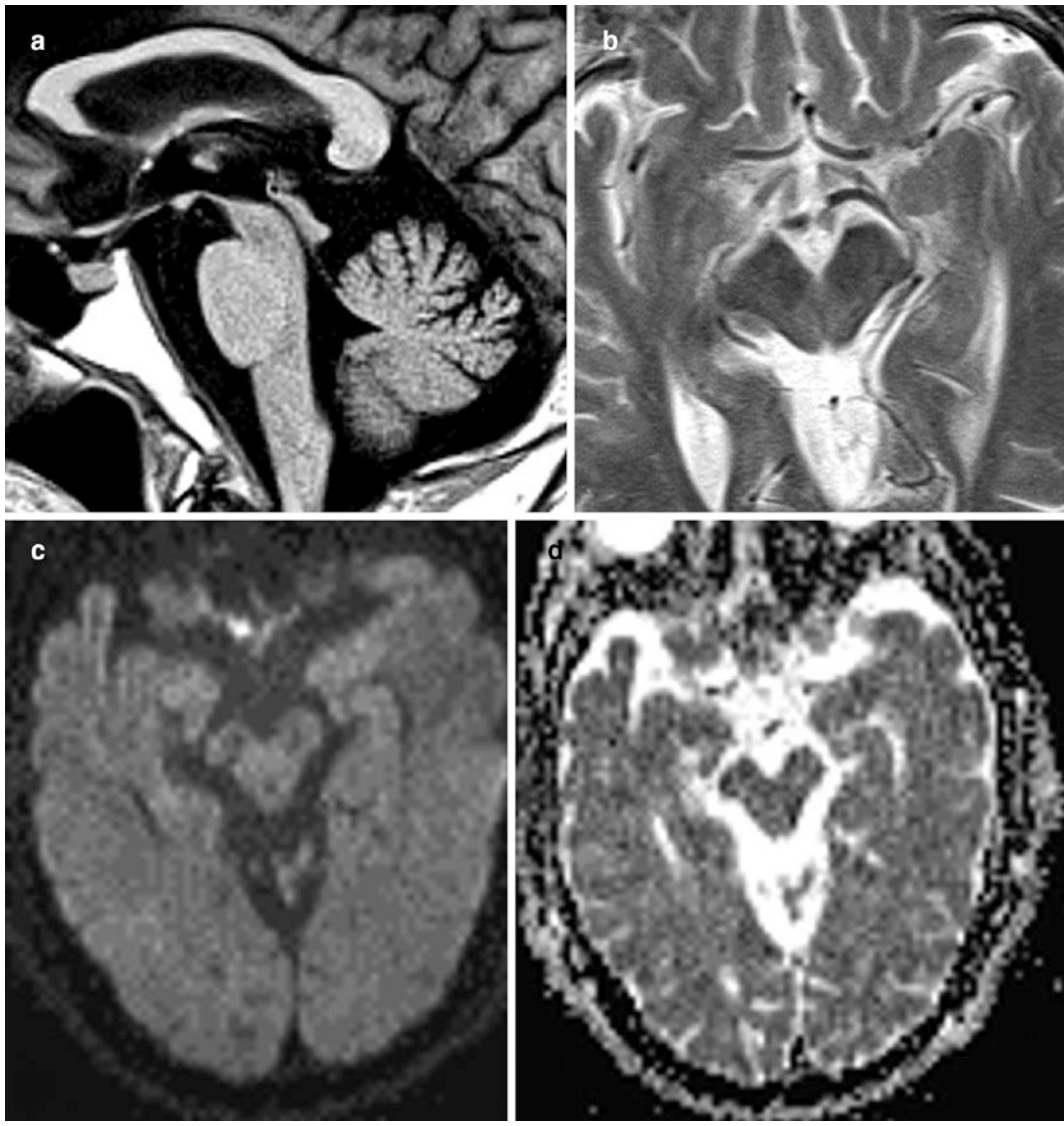


Fig. 14.3 PSP. 69-year-old. Male with PSP cardinal features including pseudobulbar palsy, rigidity, bradykinesia, masked facies, and ocular paresis with down and up gaze. Sagittal T1 (**a**) and axial T2 (**b**), trace DWI (**c**) and ADC map (**d**) with midbrain tegmental atrophy and subtle T2 hyperintensity

[36]. Core clinical features are fluctuating cognition, recurrent visual hallucinations, and parkinsonism, which distinguish LBD from AD. Main differential diagnostic considerations of LBD are Parkinson's disease with dementia (PDD) and AD. Diagnostic criteria indicate that dementia should occur before or concurrently with parkinsonism to diagnose LBD [37], while PDD is diagnosed when parkinsonism is present for 12 months or more before the onset of dementia [38]. Imaging provides indicative diagnostic biomarkers of LBD, such as reduced dopamine transporter uptake in the basal ganglia on SPECT or PET, preserved medial temporal lobe volume on structural imaging and low SPECT/PET brain uptake in the occipital cortex [36]. The characteristic pathologic lesion in LBD is the Lewy body (LB) cytoplasmic neuronal inclusion, which is immunoreactive to the presynaptic protein α-synuclein [39]. Therefore,

LBD is counted among the α-synucleinopathies together with PD and multiple system atrophy (MSA). Cortical LBs progression starts in the amygdala, then spreads to the limbic cortex and finally to the neocortex [40]. Apart from LBs, other histopathological features of LBD are Lewy-related neurites, AD-type pathology (plaques and tangles), spongiform changes, and synapse loss [41].

14.2.1 Imaging

Atrophic changes are less conspicuous and differently distributed in LBD compared to AD. Volume loss in LBD involves the dorsal midbrain, hypothalamus, and substantia innominata with sparing of the hippocampus and temporo-parietal cortex [42]. In comparison with PDD, in LBD there is more frontotemporal gray matter atrophy that correlated with neuropsychological impairment [43]. Occipital hypoperfusion and hypometabolism in LBD have been reported using SPECT and FDG-PET, respectively [44] (Fig. 14.4). Dopaminergic dysfunction assessed with SPECT or PET has become a suggestive feature of the diagnosis of LBD under the consensus criteria. LBD and PDD patients display severely reduced dopaminergic uptake in the caudate and putamen compared to controls and AD patients [45].

14.2.2 DTI

LBD is characterized by increased ADC values in the precuneus [46]. Using tract-based spatial statistics (TBSS), a voxelwise approach to DTI data in the style of VBM, LBD displayed lower FA of parieto-occipital white matter compared to controls with significantly fewer changes in frontal regions. AD subjects on the other hand had more diffuse reductions in FA on both sides of the central sulcus. Mean diffusivity (MD) changes were widespread in both conditions. The DTI changes in LBD correlated with episodic memory, letter fluency, and parkinsonian signs [47]. DLB is characterized by a loss of parieto-occipital white matter integrity (lower FA) with associated cortical glucose hypometabolism [48].

14.3 Parkinson's Disease (PD)

Parkinsonism is defined as bradykinesia, in combination with either rest tremor, rigidity, or both and is the prerequisite for clinical diagnosis of PD. Non-motor manifestations of PD such as anosmia, sleep disturbance, orthostatic hypotension, and cognitive impairment are also included in the diagnostic criteria. Movement Disorder Society PD criteria [49] use motor parkinsonism as the core feature of the diagnosis, defined as bradykinesia plus rest tremor or rigidity. After determination of parkinsonism, diagnosis of PD uses three categories of diagnostic features: absolute exclusion criteria (which rule out PD), red flags (which must be counterbalanced by additional supportive criteria to allow diagnosis of PD), and supportive criteria (positive features that increase confidence of the PD diagnosis). Normal functional imaging of the presynaptic dopaminergic system is one of the absolute exclusion criteria, whose presence rules out PD. 75–95% of patients diagnosed with PD by clinical experts have their diagnosis confirmed on autopsy [49]. Sporadic PD involves multiple neuronal systems and results from changes developing in a few susceptible types of nerve cells. Essential for neuropathological diagnosis are α-synuclein-immunopositive Lewy neurites and Lewy bodies. The pathological process starts in the dorsal motor nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus. Thereafter, the disease process propagates along the brain stem with an ascending course leading to the midbrain [50]. Degeneration of nigrostriatal neurons is responsible for the classical motor manifestations of PD. The underlying pathophysiology includes α-synuclein deposition in Lewy bodies, found in residual neurons in affected areas such as the substantia nigra pars compacta (SNpc), and in dystrophic neurons in striatal or cortical regions (Lewy neurites).

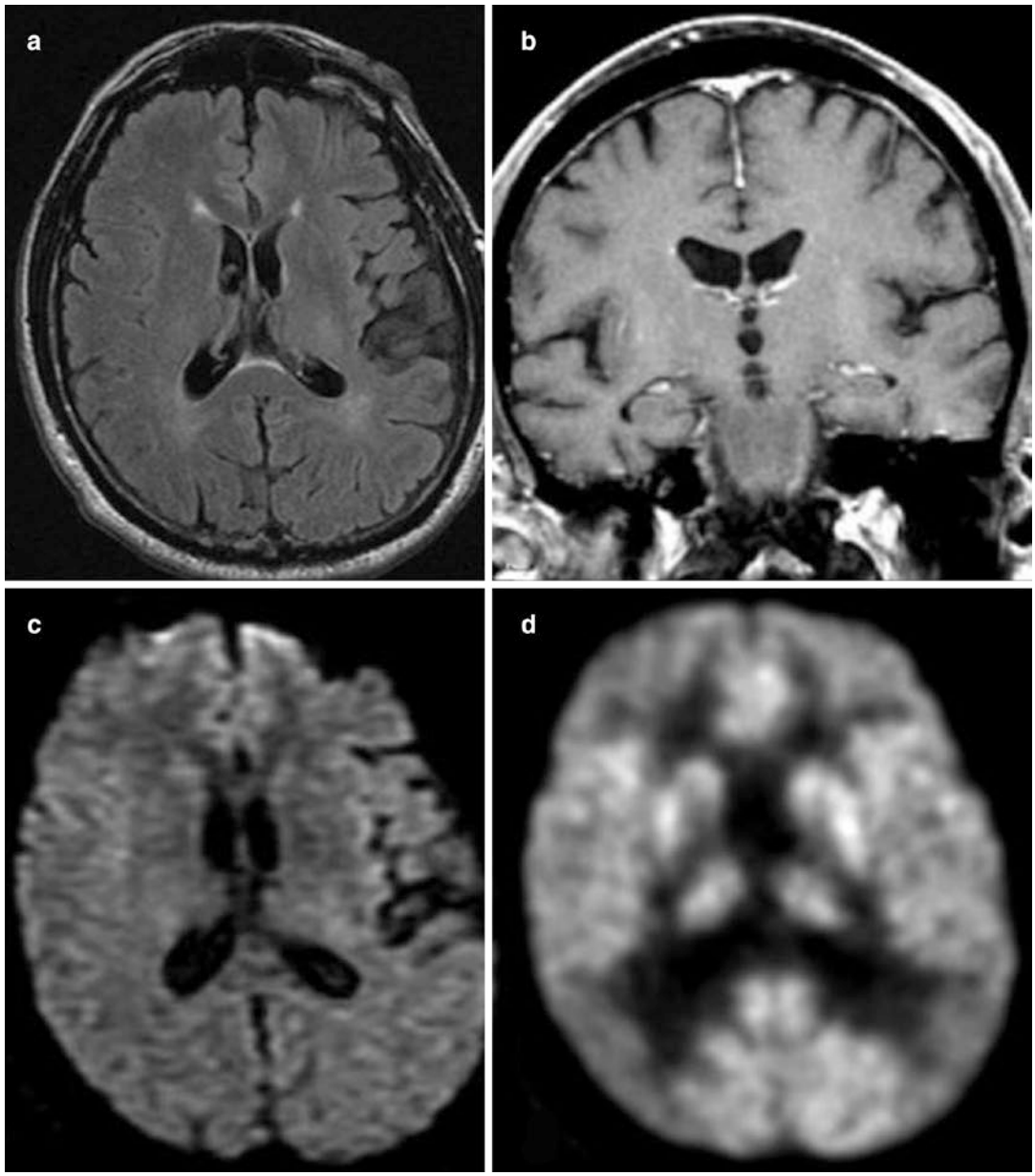


Fig. 14.4 75-year-old male with probable Lewy body disease. Axial FLAIR (**a**) and coronal T1 (**b**) show lack of obvious cortical atrophy or vascular brain damage. Trace DWI (**c**) is unremarkable. Axial FDG PET (**d**) with bilateral temporo-occipital hypometabolism

14.3.1 Imaging

Historically, MRI has contributed little to the assessment of PD, except to rule out vascular lesions. Different metabolic imaging approaches may be used to assess the altered function of the nigrostriatal dopaminergic nerve terminals. The most widely used approach is a marker for the dopamine transporter (DAT) (Fig. 14.5). Several positron or photon-emitting molecules are available with PET or SPECT, respectively. Striatal DAT binding correlates with loss of nigrostriatal dopamine terminals, but only correlates with nigral neuron density when neuron loss does not

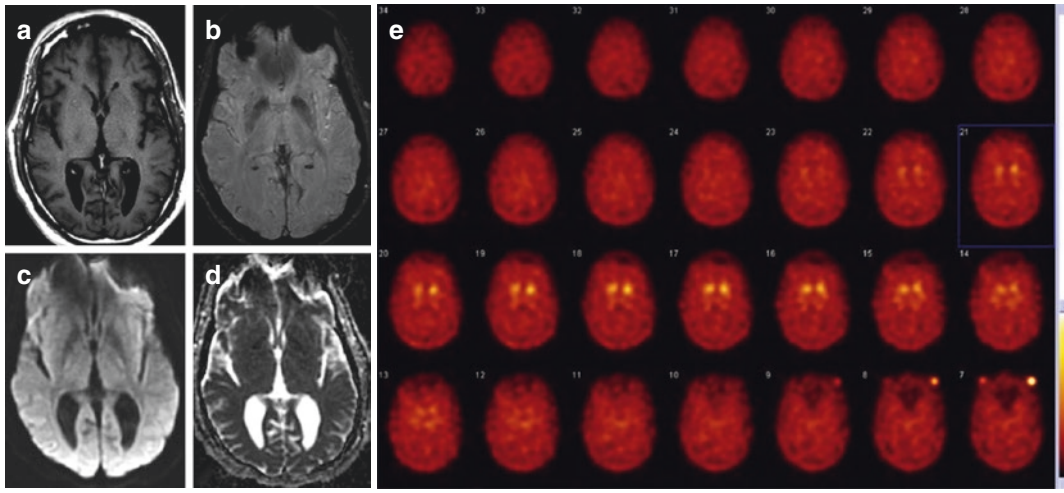


Fig. 14.5 59-year-old man with Parkinson's disease. Axial T1 (**a**) and SWI (**b**) at the level of the basal ganglia. Trace DWI (**c**) and ADC map (**d**) are grossly unremarkable. [I-123] FPCIT DAT imaging (**e**) with right greater than left decreased uptake in the bilateral putamen

exceed 50%. Therefore, striatal DAT may not reflect disease progression beyond the mild-to-moderate stage [51].

Advanced MRI approaches have disclosed potential markers that are useful in research and clinical diagnosis of PD. The loss of the normal nigrosome-1 hyperintensity against the dark SN on iron-sensitive SWI constitutes the basis of the "swallow tail" sign in PD [52]. Using SWI MRI, healthy controls consistently display a hyperintense, ovoid area within the dorsolateral border of the otherwise hypointense SNpc. Across studies, the signal loss in this region had a high sensitivity (79–100%) and specificity (84.6–100%) to separate PD from HC [53]. T1-weighted images are sensitive to the paramagnetic properties of neuromelanin, a pigment contained in the SNpc that appears as an area of high signal intensity on T1-weighted images. The neuromelanin pigmented neurons of the SNpc are particularly vulnerable to neurodegeneration in PD where the neuronal loss is earliest in the ventral–lateral tier of the SN, resulting in a rostro-caudal gradient of reduction of nigrostriatal projections. T1-weighted FSE imaging has consistently demonstrated significant reduction in the neuromelanin-associated T1 hyperintensity of the SN in PD compared to healthy controls [54].

14.3.2 DWI in PD

In a meta-analysis [55] of 39 studies on DTI in PD vs. controls, five anatomic regions demonstrated significant differences between PD patients and healthy controls in FA and MD. Four of these regions showed a decrease of FA and an increase of MD: the SN, the corpus callosum, the cingulate, and the temporal cortices. On the other hand, the corticospinal tract showed an opposite change: increased FA and decreased MD.

14.4 Multiple System Atrophy (MSA)

MSA is a sporadic, adult-onset neurodegenerative disease that presents with a combination of parkinsonism, cerebellar ataxia, and autonomic failure. Based on the dominant clinical presentation, it is subdivided into MSA-P, the parkinsonian phenotype that is the most common, MSA-C, the cerebellar type, and MSA-A or autonomic failure. Olivo-ponto-cerebellar atrophy and striatonigral degeneration are found at postmortem examination [56]. Neurodegenerative changes also involve the central autonomic nuclei, including the hypothalamus, noradrenergic, and sero-

toninergic brain-stem nuclei, the dorsal nucleus of the vagus, nucleus ambiguus, and intermediolateral columns of the spinal cord. Proteinaceous oligodendroglial cytoplasmic inclusions (Papp–Lantos bodies) are the histologic hallmark of MSA. The constituent of these inclusions is misfolded α-synuclein; therefore, MSA is counted among the α-synucleinopathies together with PD and LBD, although in the former two diseases α-synuclein deposits are primarily intraneuronal.

On conventional MRI, MSA-P exhibits putaminal atrophy, T2* hypointensity, and "slit-like" marginal FLAIR hyperintensities (Fig. 14.6), whereas MSA-C shows atrophy of

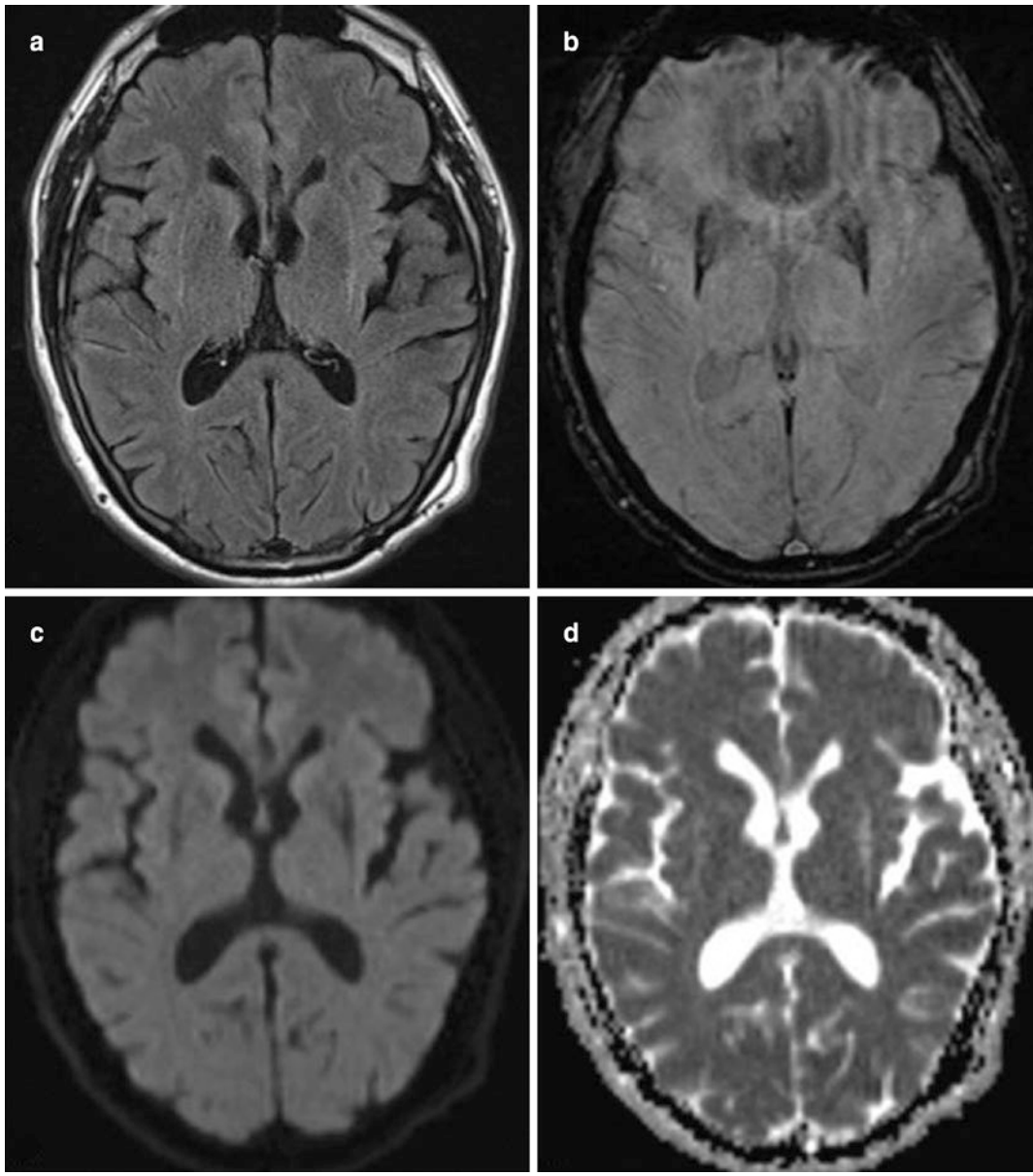


Fig. 14.6 63-year-old man with **MSA-P**. Diagnosed with parkinsonian syndrome 4 years before without benefit from carbidopa/levodopa. Axial FLAIR (**a**) and SWI (**b**) with lateral putaminal hyper and hypointensity, respectively. Trace DWI (**c**) and ADC map (**d**)

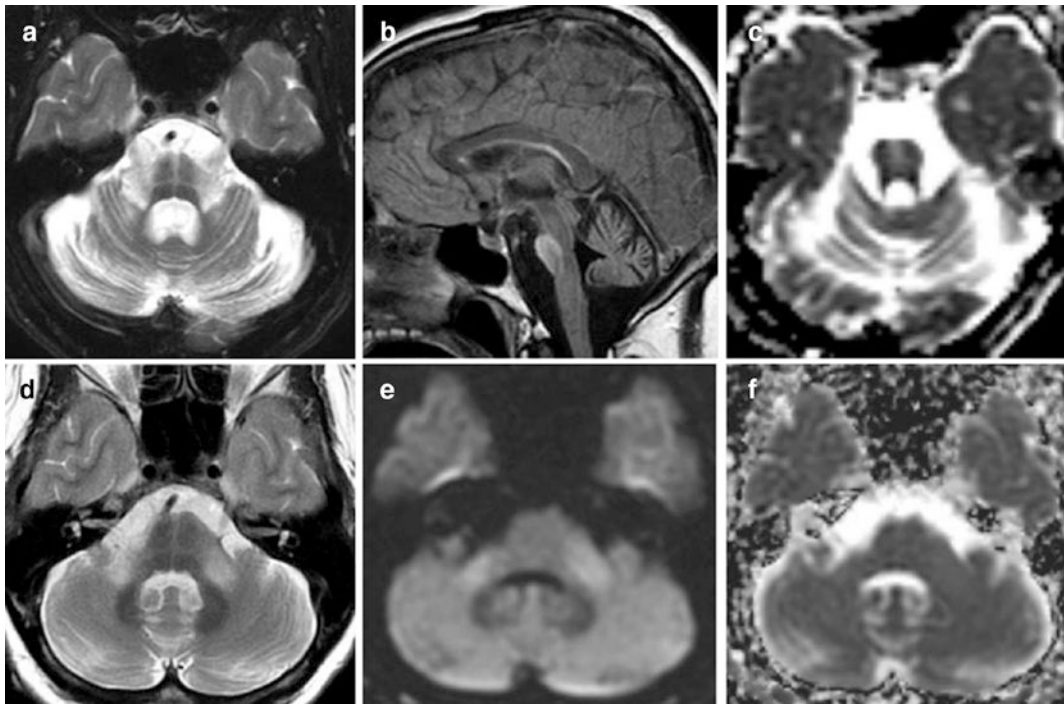


Fig. 14.7 53-year-old woman with a 5-year history of gradually progressive cerebellar ataxia, dysarthria, and balance difficulties. Axial T2 with hot cross bun sign (**a**), sagittal FLAIR with pontine atrophy and hyperintensity (**b**), and ADC map (**c**). Imaging 3 years 9 months earlier with T2 hyperintensity of middle cerebellar peduncles (**d**) with high signal on trace DWI (**e**) ADC map (**f**)

the lower brainstem, pons, middle cerebellar peduncles, vermis, with pontine cruciform T2-weighted hyperintensity (hot cross bun sign) (Fig. 14.7) [52]. SWI signal values of the putamen and pulvinar show more iron deposition in MSA-P, differentiating MSA-P from PD [57]. As already mentioned for PD, the loss of the dorsolateral normal nigral SWI hyperintensity was seen unilaterally in all patients with MSA or PSP, in 83 of 90 patients with PD, but only in 1 of 42 controls; therefore, it has been proposed as an imaging biomarker for neurodegenerative parkinsonism [58].

14.4.1 DWI in MSA

A recent meta-analysis of putaminal diffusivity on high-field DWI showed discrimination of PD from MSA-P, which has higher ADC values, with sensitivity of 90 and 93% specificity [59]. DTI reveals lower FA and higher MD in the middle cerebellar peduncles of MSA patients, while diffusivity is increased at the decussation of the superior cerebellar peduncles in PSP [60].

14.5 Frontotemporal Lobar Degeneration

14.5.1 Introduction

Frontotemporal lobar degeneration (FTLD) includes heterogeneous neurodegenerative disorders clinically characterized by progressive behavioral changes, language disturbances and focal brain atrophy. The average age at clinical onset is 50–60 years, i.e., younger than for sporadic AD. FTLD encompasses three main clinical syndromes: behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA) [61].

Primary progressive aphasia includes three clinical subtypes (non-fluent, semantic, and logopenic variants). Furthermore, there is a strong association between FTLD and amyotrophic lateral sclerosis (ALS): half of ALS patients have cognitive impairment of the frontal type, while 50% of FTLD patients have clinical features of ALS [62].

FTLD is pathologically heterogeneous, but an early common feature is gross circumscribed atrophy of the frontal or anterior temporal lobes. The pattern of atrophy shown by clinical imaging correlates with the specific clinical syndrome. Prefrontal atrophy leads to bvFTD, anterior temporal atrophy correlates with SD and left perisylvian atrophy with PNFA. From the molecular standpoint, three subtypes of FTLD are recognized [63]: (1) tau-positive pathology (Pick's disease); (2) tau-negative with ubiquitin-positive inclusions of transactive response DNA-binding protein of 43 kDa (TDP-43) (the most common type of FTLD diseases); and (3) tau-negative, ubiquitin-negative pathology.

14.5.1.1 Imaging

There is characteristic atrophy on clinical CT and MRI studies which correlates with the clinical syndrome [64]. In bvFTD there is an anteroposterior gradient of atrophy involving the frontal and temporal lobes with sparing of the parietal and occipital lobes, often asymmetrical (Fig. 14.8). A meta-analysis of VBM studies in bvFTD demonstrated significant gray matter loss in prefrontal regions compared to controls, with the most significant changes in the medial frontal lobes with volume reductions also in the insula and striatum [65]. However, hippocampal and amygdalar atrophy that are characteristic of AD are also seen with bvFTD [66].

SD shows consistent left anterior temporal lobe atrophy, also involving inferior and mesial temporal lobe regions, with an anteroposterior gradient (more atrophy seen anteriorly) which distinguishes SD from AD [67] (Fig. 14.9). PNFA leads to cortical thinning and atrophy of the left inferior frontal lobe including Broca's area, superior temporal lobe, and insula. The patterns of cortical thinning

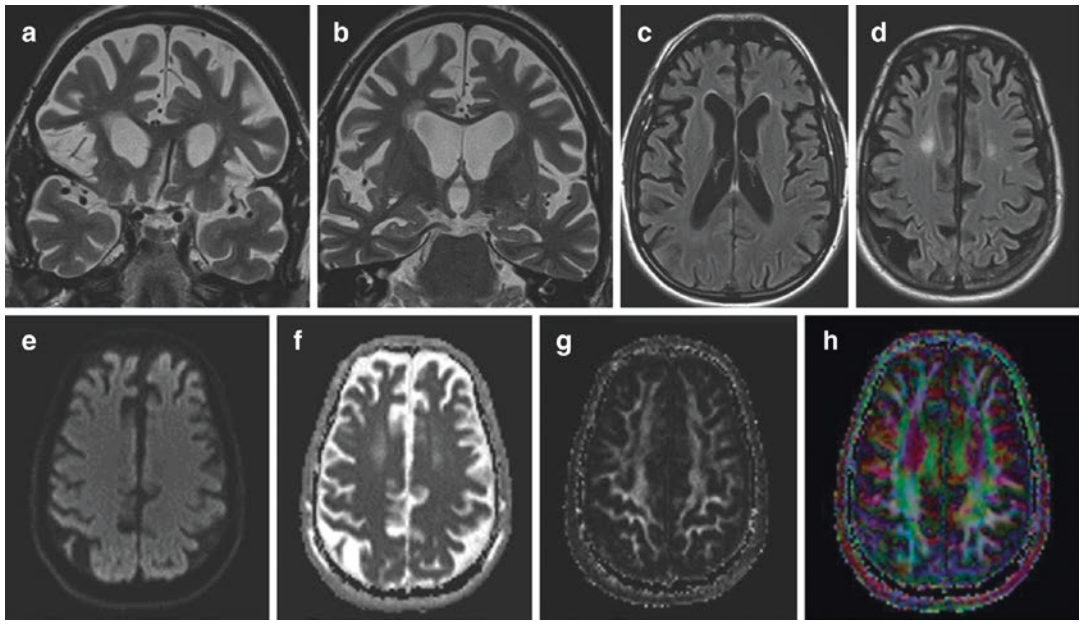


Fig. 14.8 53-year-old man who, in less than 1 year, progressed from cognitively normal to first behavioral changes followed by broad cognitive deficits including prominently reduced fluency. (**a**, **b**) Coronal T2 and (**c**, **d**) axial FLAIR show bilateral frontotemporal cortical atrophy with wide sylvian fissures. (**e**) trace DWI, (**f**) ADC map, (**g**) FA map, (**h**) DTI color map

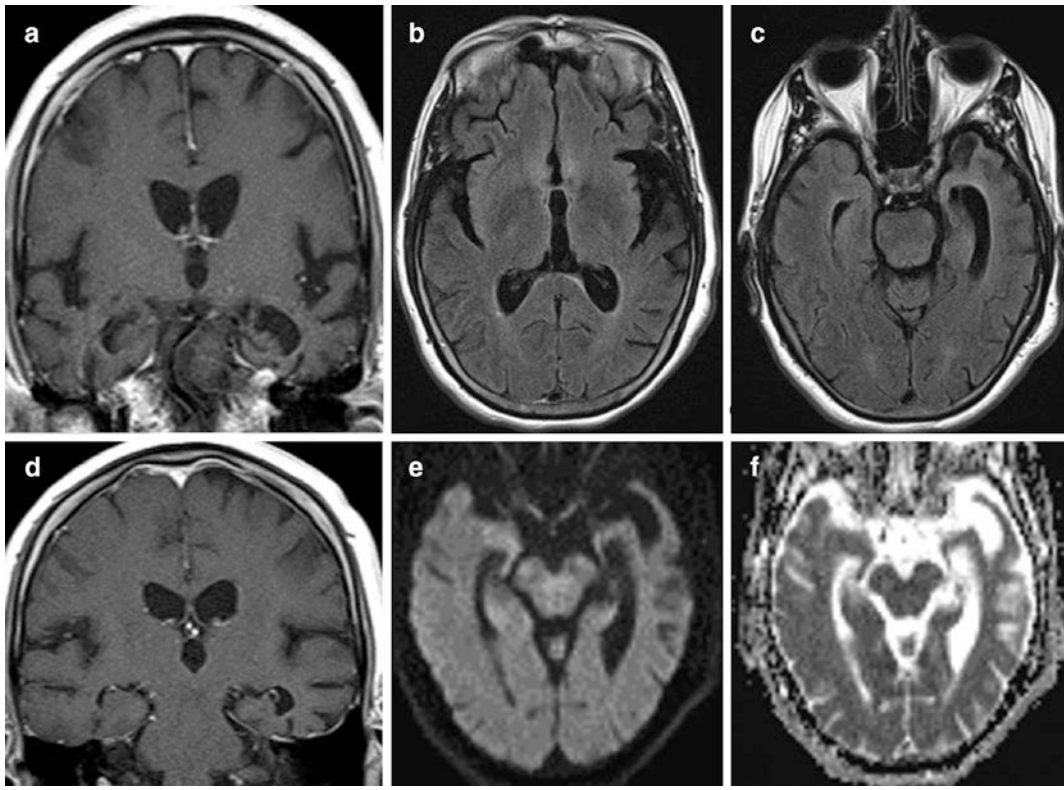


Fig. 14.9 61-year-old woman with frontotemporal dementia, behavioral variant with significant semantic deficits that developed later in the course of the disease. (**a**, **d**) Coronal T1, (**b**, **c**) axial FLAIR, (**e**): trace DWI and (**f**) ADC map show left perisylvian and prominent left hippocampal atrophy

differ between PNFA and SD, with more frontal and parietal atrophy in PNFA vs. bilateral temporal cortical atrophy in SD [68]. Nuclear medicine clinical imaging studies in FTLD demonstrate abnormal brain perfusion and glucose metabolism using SPECT and PET, respectively. A pattern of bilaterally reduced frontal CBF in the absence of parietal hypoperfusion is characteristic in pathologically confirmed FTLD [64].

14.5.1.2 DTI

The diffusivity of gray matter is increased in regions affected in FTLD, suggesting disruption of the cytoarchitecture of remaining tissue. Furthermore, damage was identified in white matter tracts that interconnect affected regions [69]. DTI studies in bvFTD showed bilateral involvement of white matter tracts connecting the frontal lobes such as the anterior cingulum, superior longitudinal fasciculus, and genu of the corpus callosum [70]. PPA patients displayed more focal white matter involvement compared to bvFTD, with differential involvement in the nonfluent, semantic, and logopenic variants of PPA. White matter disorganization in FTLD likely results from axonal degeneration secondary to neuronal body death, as supported by the correlation between white matter changes and cortical atrophy.

14.6 Vascular Dementia

Although not considered among neurodegenerative diseases, vascular dementia is the second cause of dementia after Alzheimer's disease, causing around 15% of cases [71]. Pathological studies showed that subcortical ischemic vascular disease (SIVD), rather than large cortical infarcts, accounts for most cases of vascular dementia

[72]. SIVD results from small-vessel disease, with arteriolar occlusion and lacunar infarctions or widespread incomplete infarction of white matter due to critical stenosis of medullary arterioles and hypoperfusion. Binswanger disease represents the most severe form of SIVD with sparing only of the subcortical U fibers (Fig. 14.10).

The imaging appearance of the progressively confluent white matter T2 hyperintensities with facilitated DWI is best described as leukoaraiosis, i.e., white matter rarefaction [73]. With progressive aging, mixed dementia that results from a combination of neurodegenerative and vascular lesions becomes more prevalent than pure forms [74]. Cerebral amyloid angiopathy is highly prevalent in these pathologically mixed dementia cases, while lacunar infarctions are characteristic of SIVD [74]. Although rare among cases of vascular dementia, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) has a defined genetic cause from a frameshift mutation in the notch gene on chromosome 19 [75].

14.7 Fragile X Syndrome (FXS)

FXS is the most common cause of inherited intellectual disability and the leading form of the monogenic cause of autism. FXS is caused by a triplet expansion that inhibits expression of the mental retardation type 1 (FMR1) gene; its gene product, FMRP, regulates mRNA metabolism in the brain. Expansion in this triplet sequence gives rise to FXS, which is the prototype of unstable triplet expansion disorders [76]. Fragile X FMR1 gene premutation (with number of CGG repeats ranging from 55 to 200) is the first single-gene cause of primary ovarian failure and one of the most common causes of ataxia (fragile X-associated tremor/ataxia syndrome [FXTAS]) [77].

Neuroimaging features include T2 hyperintense lesions in the middle cerebellar peduncles as the main imaging criterion and cerebellar white matter hyperintensities, cerebellar and callosal atrophy with ventricular enlargement and white matter T2 hyperintensities [78]. Hyperintensity of the splenium of the corpus callosum is also frequently observed and can suggest the diagnosis even in the absence of hyperintensities of the brachium pontis [79] (Fig. 14.11).

14.8 Creutzfeldt-Jakob Disease (CJD)

CJD is one of the prion diseases characterized by rapidly progressive degenerative dementia, myoclonus, and ataxia. However, the initial clinical presentation is sometimes nonspecific and variable such as visual disturbance (Heidenhain variant), deafness, and hemiparesis [80]. The cause of neurodegeneration is thought to be an accumulation of an abnormal form of human prion protein (infectious proteinaceous scrapie particles, PrP^{Sc}). There are four forms of CJD: sporadic, iatrogenic, familial, and variant [81]. Iatrogenic cases include contaminated neurosurgical instruments, administration of human growth hormone, cadaver-derived gonadotrophin, and dura matter (Fig. 14.12) and corneal grafts [81]. Histological features include spongiform degeneration of the gray matter, characterized by clustered, 5–25 micrometer large prion protein-containing vacuoles in the neuronal and glial elements, and neuronal loss, presumably due to apoptosis and gemistocytic astrocytosis [82] (Fig. 14.13). Electron microscopy shows these vacuoles as focal swelling of neuritic processes, both axonal and dendritic swelling (cellular edema), which may cause decreased ADC [83].

DWI is the most sensitive MRI technique for diagnosing CJD, and is included in the clinical diagnostic criteria [84–87] (Fig. 14.12). Specifically, DWI or FLAIR hyperintensity in the basal ganglia (both caudate nucleus and putamen) or in at least two cortical regions (either the temporal, parietal, or occipital cerebral cortices) is one of the supportive tests for CJD diagnosis, together with detection of 14-3-3 protein in CSF

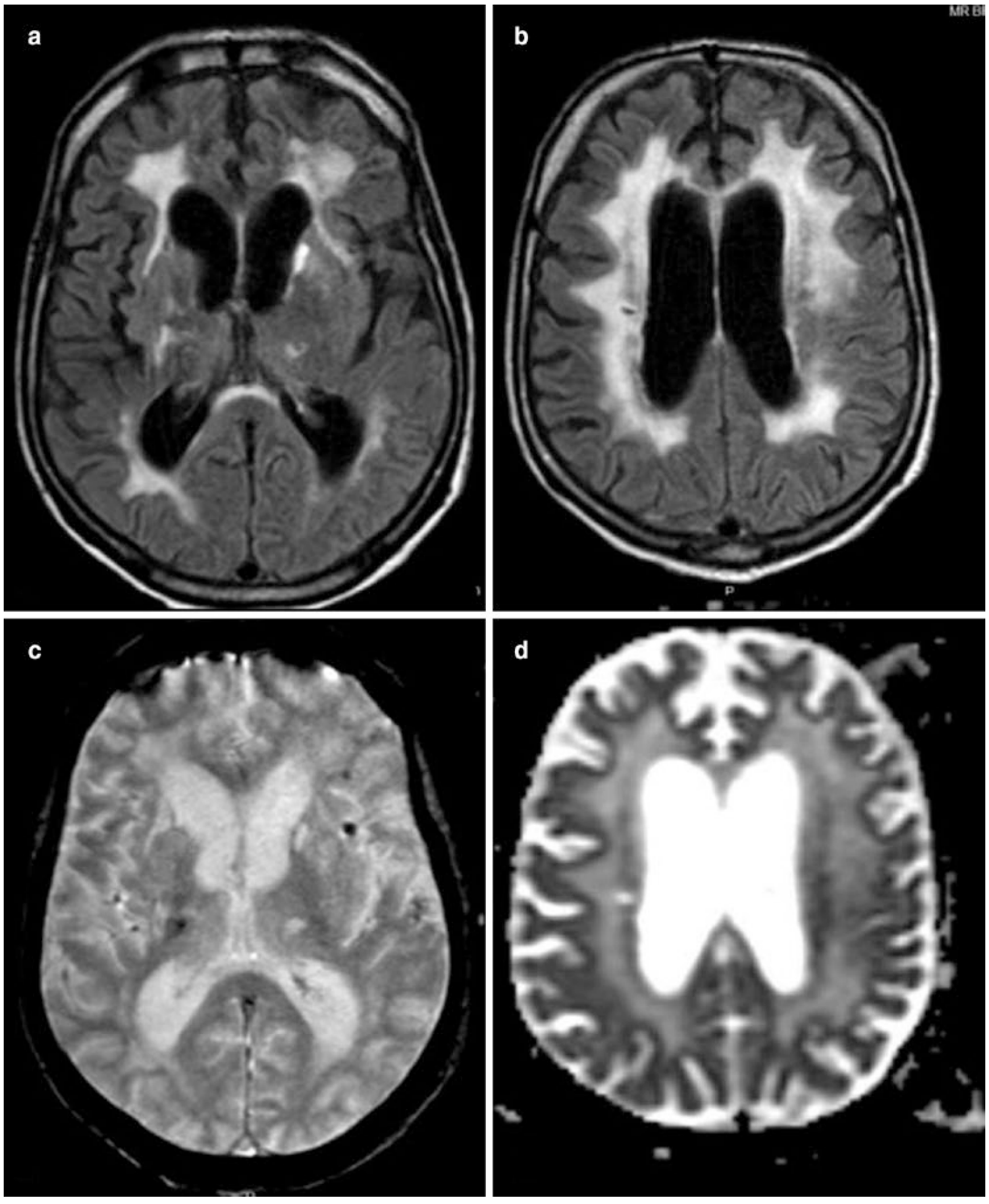


Fig. 14.10 Severe SIVD consistent with Binswanger disease. FLAIR (**a**, **b**), GRE (**c**), and ADC map (**d**) in 71-year-old male with essential hypertension and systemic vasculopathy

and presence of periodic sharp wave complexes on EEG [88] (Figs. 14.12, 14.13, and 14.14). A newer in vitro protein assay system for the detection of prion protein in CSF is real-time quaking-induced conversion assay (RT-QuIC), which has sensitivity of 80–95% and specificity of 99% for CJD diagnosis when applied in symptomatic patients in clinical setting [89].

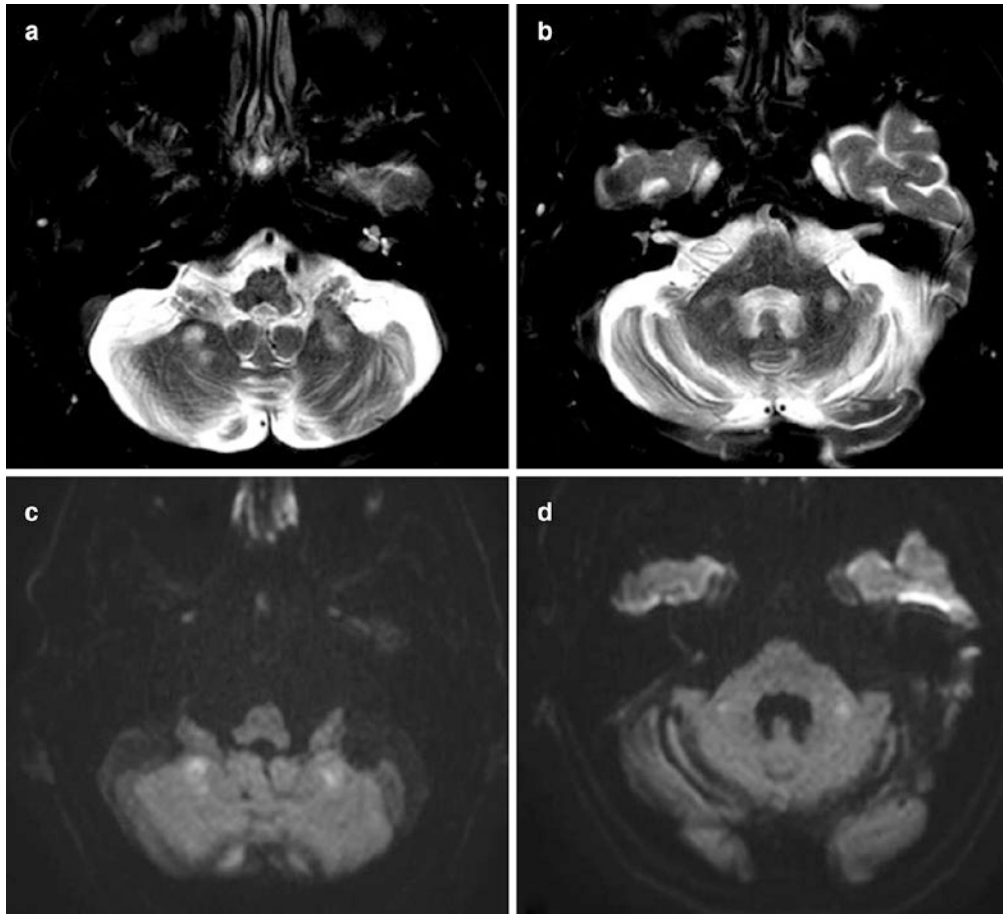


Fig. 14.11 FXS in 71-year-old man with tremor, balance issues, and cognitive impairment with maternal inheritance pattern and FXS premutation status (with 93 CGG repeats at the FMR1 gene). (**a**, **b**) Axial T2, (**c**, **d**) axial trace DWI displaying characteristic involvement of the middle cerebellar peduncles

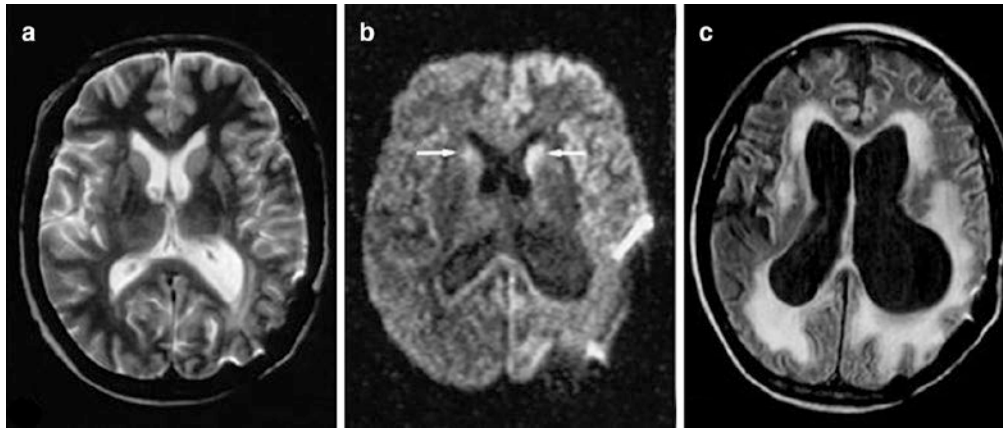


Fig. 14.12 Creutzfeldt–Jakob disease in a 57-year-old woman with progressive dementia 10 years after surgery using cadaver dura matter. (**a**) T2-weighted image shows postoperative change in the left temporo-occipital region with mild ventricular dilatation. (**b**) DW image reveals bilateral hyperintensity in the caudate nuclei (*arrows*) and mild increased signal diffusely in the left hemisphere. (**c**) A 4-month follow-up FLAIR image shows extensive white matter hyperintensity and diffuse atrophy

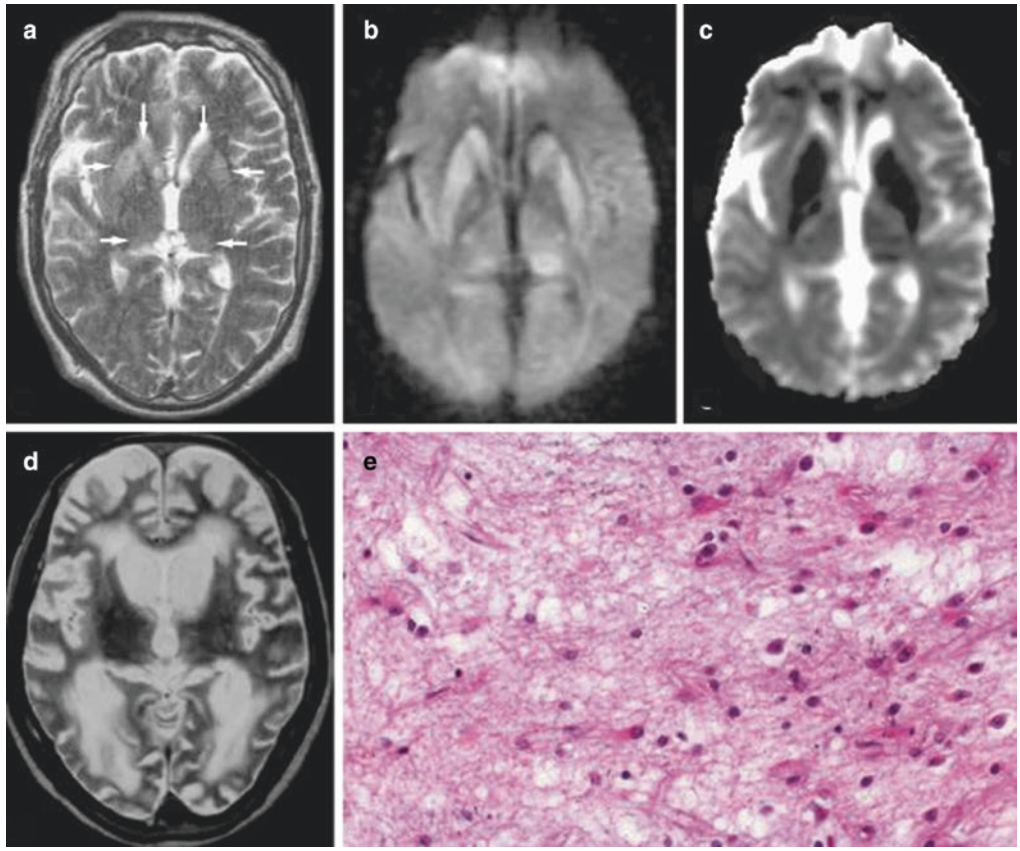


Fig. 14.13 Creutzfeldt–Jakob disease in a 51-year-old man with progressive dementia. (**a**) T2-weighted image demonstrates mild hyperintensity bilaterally in the caudate nuclei, putamina, and pulvinar of the thalami (*arrows*). (**b**) DW image clearly demonstrates these lesions as hyperintense. (**c**) ADC is decreased. (**d**) A 6-month follow-up T2-weighted image shows prominent diffuse atrophy and white matter hyperintensity. (**e**) Pathological specimen of another case shows spongiform degeneration and reactive astrocytosis. (Courtesy of Ukisu R, MD, Showa University, School of Medicine, Japan)

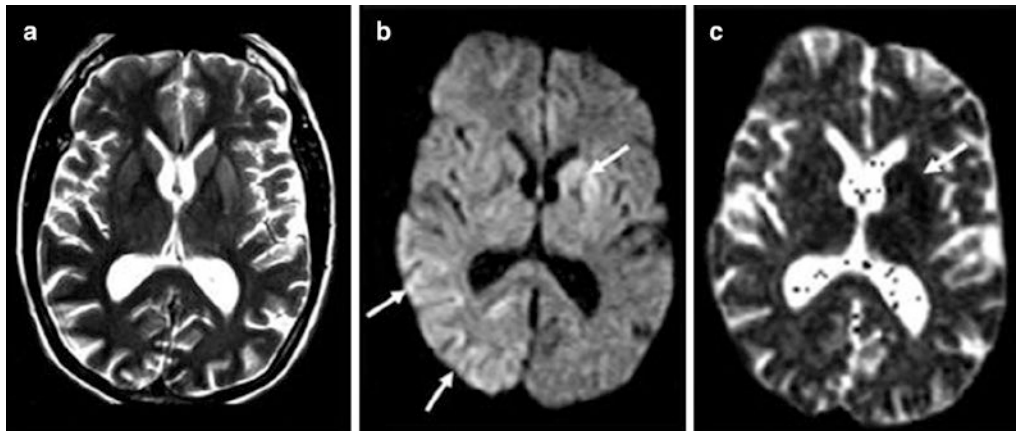


Fig. 14.14 Creutzfeldt–Jakob disease in a 58-year-old woman with altered mental status and visual symptoms (Heidenhain variant). (**a**) T2-weighted image shows questionable hyperintensities in the basal ganglia bilaterally. (**b**) DW image demonstrates hyperintensities only in the left basal ganglia (*arrows*). Hyperintense lesions are also noted in the right temporo-occipital cortices, which does not correspond to a single vascular territory (*arrows*). (**c**) ADC is partially decreased in these lesions (*arrows*)

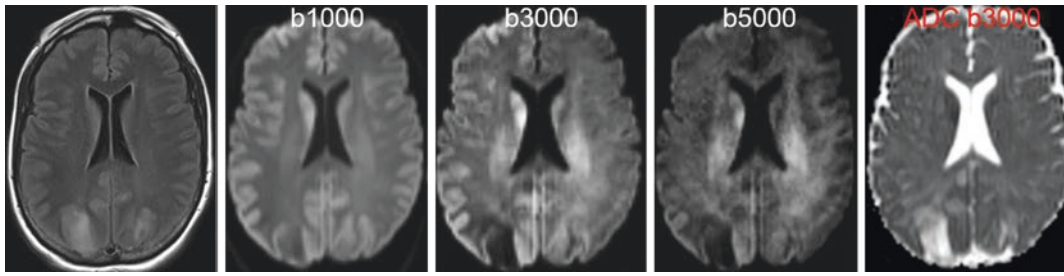


Fig. 14.15 Diffusion restriction in the right caudate and bilateral cerebral hemispheres at three different b values in a CJD case with concurrent PRES

MRI is very important for diagnosis in the context of the clinical criteria because 10% of cases are RT-QuIC negative [89]. T2-weighted and FLAIR images show subtle hyperintense lesions in the cerebral cortex and bilateral basal ganglia in patients with CJD, usually seen 2–5 months after the onset of symptoms. The lesions often involve the bilateral thalami (pulvinar sign) and periaqueductal areas in patients with variant CJD [90], but this finding is also seen in sporadic CJD [91] (Fig. 14.13) Cerebral white matter T2 hyperintensity is considered to be primary degeneration, and first occurs in the periventricular area 4–5 months after the onset and rapidly extends to the deep and subcortical white matter during the following several months [92].

The cortical involvement is usually asymmetric, which does not correspond to arterial territories. Bilateral basal ganglia or thalamic involvement is usually symmetric, but can be asymmetric (Figs. 14.12, 14.13, and 14.14). The lesions are hyperintense on DW images and often associated with decreased ADC [83, 87, 93]. High *b* values of 2000 s/mm^2 or 3000 s/mm^2 [94] have been found to be more sensitive to detect spongiform pathology in variant and sporadic CJD (Fig. 14.15). Caution should be exercised, though, when comparing DWI studies acquired at different b values because higher b factors change the absolute value of the measured ADC, which is important for lesion detection [95]. In the late stages, abnormal hyperintense signals disappear with prominent brain atrophy, histologically representing neuronal loss and marked fibrillary gliosis [93].

14.9 Neuronal Intranuclear Inclusion Disease (NIID)

Neuronal intranuclear inclusion disease (NIID) is a recently described, rare neurodegenerative disease pathologically characterized by eosinophilic hyaline intranuclear inclusions in the central, peripheral, and autonomic nervous system and visceral organs [96, 97]. NIID has been considered a heterogeneous disease because of the highly variable clinical manifestations, with sporadic and familial forms. Adult-onset NIID develops with progressive dementia, but may also have stroke-like episodes and seizures. Muscle weakness and sensory disturbance have also been observed, particularly in early-onset cases.

On MRI, there is high signal intensity in the corticomedullary junction on diffusion-weighted images in both sporadic and familial NIID cases, which is a strong clue to the diagnosis (Fig. 14.16). Spongiotic white matter changes on pathology co-localize with subcortical DWI high signals [98]. Other findings are cerebellar atrophy and high FLAIR signal in the paramedian cerebellar hemispheres [99]. Biphasic perfusion changes with initially reduced blood flow followed by hyperperfusion have been reported [96]. Skin biopsy is diagnostic with demonstration of eosinophilic, ubiquitin-immunoreactive, and p62-immunoreactive intranuclear inclusions.

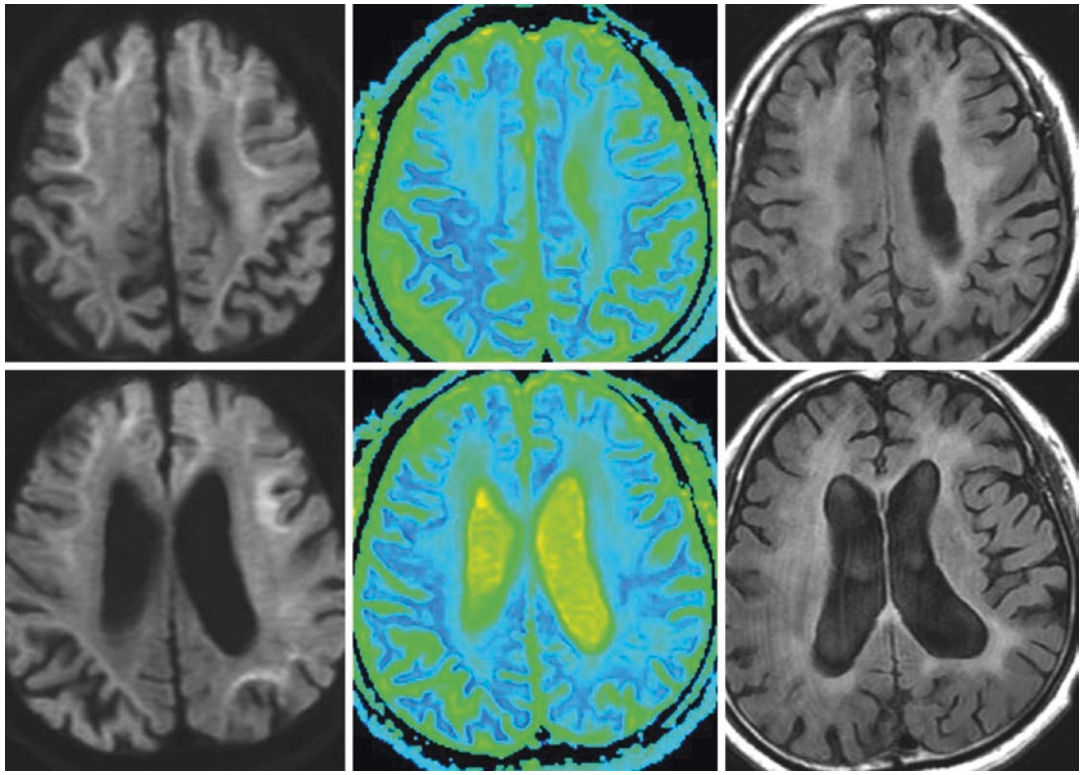


Fig. 14.16 NIID. 60-year-old male with aphasia and incomplete right hemiparesis 2 years before onset of dementia. Subcortical white matter restricted diffusion on color ADC map. Case courtesy of Dr.Takashi Abe MD, PhD, Department of Radiology, Faculty of Medicine, Tokushima University, Japan

14.10 Hereditary Diffuse Leukoencephalopathy with Axonal Spheroids (HDLS)

HDLS is a rare, autosomal dominant disease clinically characterized by adult onset of progressive dementia and behavioral changes, apraxia, apathy, impaired balance, parkinsonism, spasticity, and epilepsy [100]. The underlying genetic defect has been linked to mutations in the colony stimulating factor 1 receptor (CSF1R) gene, primarily expressed in microglia [101]. On imaging, patients display frontal T2 hyperintensity in the periventricular, deep, and subcortical white matter, small white matter calcifications, thinning of the corpus callosum and T2 hyperintensity of the corticospinal tracts with central atrophy, but no significant gray matter abnormality [102]. MRS revealed decreased NAA and glutamate concentrations in the affected white matter, which probably reflected neuronal loss [103]. Differential diagnoses include multiple sclerosis [104], cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and other leukoencephalopathies such as late-onset metachromatic leukodystrophy (MLD), X-linked adrenoleukodystrophy (x-ALD), and Krabbe disease [105]. Microscopically, the white matter abnormalities are characterized by loss of myelin and axons and the presence of numerous round to sausage-shaped axonal swellings: the neuroaxonal spheroids [106]. On DWI weighted imaging, small, persistent, and increasing foci of diffusion restriction are seen within the white matter lesions, presumably reflecting intramyelinic edema in regions of neurodegeneration (Fig. 14.17) [107]. Thus, persistent foci of restricted diffusion constitute a characteristic imaging feature of HDLS [100, 102, 105], not seen in other leukoencephalopathies.

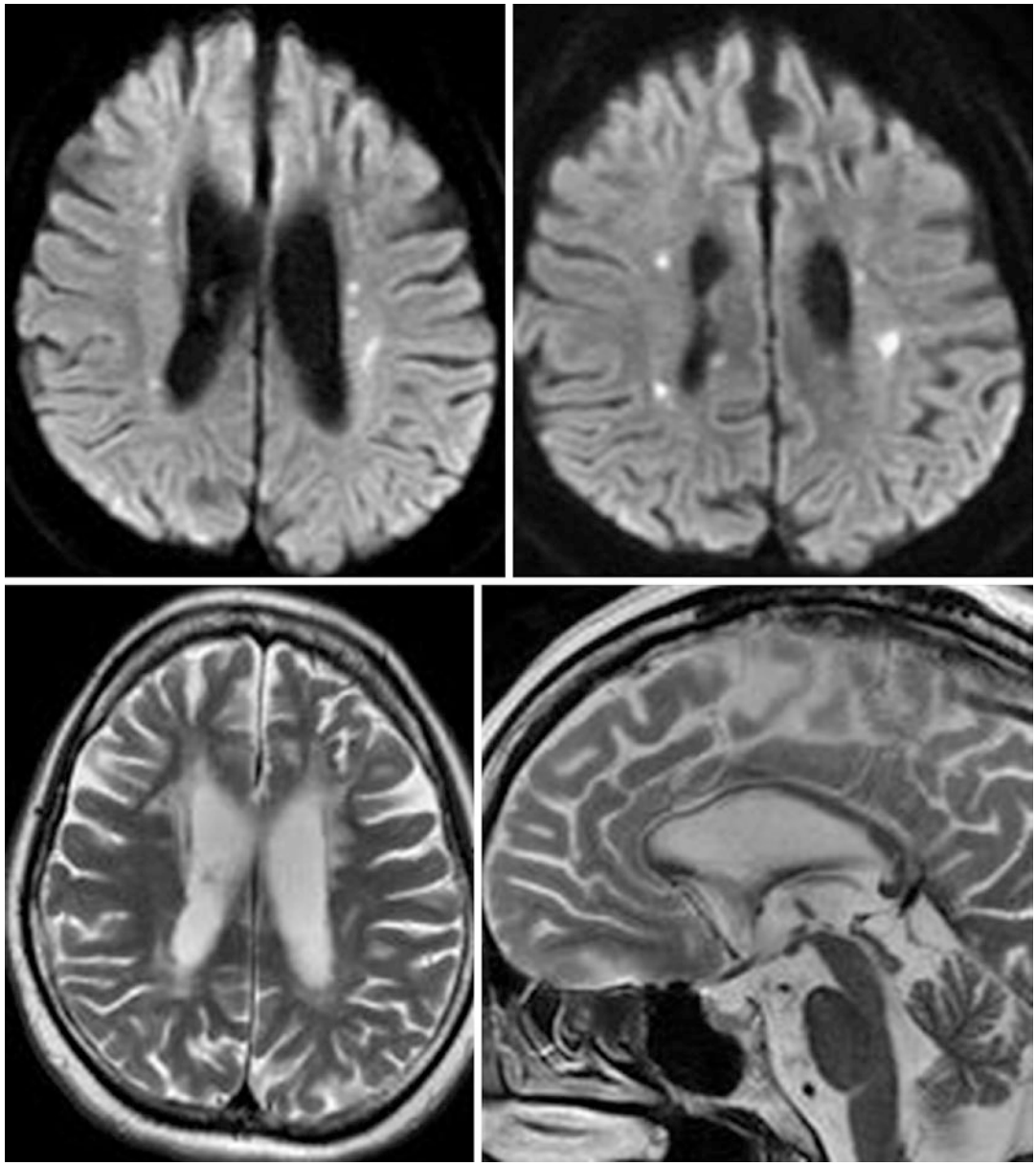


Fig. 14.17 HDLS 55-year-old female with dementia: Foci of longstanding restricted diffusion in the deep white matter (top) and T2 hyperintensity with volume loss of the centrum semiovale and genu (bottom). (Case courtesy of Dr.Takashi Abe MD, PhD, Department of Radiology, Faculty of Medicine, Tokushima University, Japan)

14.11 Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative, heterogeneous syndrome that is currently conceptualized as a continuum between frontotemporal dementia and motor neuron disease and is strongly associated with expansion mutations in the *C9orf72* gene [108]. ALS affects both upper and lower motor neurons and their projections. It often afflicts middle-aged patients and is characterized by progressive muscle weakness, limb and truncal atrophy associated with bulbar signs and symptoms. The disease progression is relentless, and half of the patients die within 3 years. Degeneration of upper motor neu-

rons usually starts in the primary motor cortex, and secondary degeneration of motor fibers and gliosis occurs along the corticospinal tract with TDP-43 pathology.

MR images of ALS are characterized by high T2 signal along the large myelinated pyramidal tract fibers in the posterior limb of the internal capsule and cerebral peduncles. On DW imaging there are typically increased ADC values and decreased fractional anisotropy in the corticospinal tracts [109]. DTI is useful in analyzing the extent and severity of axonal degeneration quantitatively in ALS (Fig. 14.18) [110–113]. Compared to controls, ALS patients showed a significant decrease of FA and fiber length and density in the corticospinal tracts (CSTs) and in the corpus callosum (CC) [114] and in other white matter regions including the brainstem [115]. Clinical functional scales correlate with corticospinal DTI measures along the clinical spectrum of *C9orf72* mutation carriers [113]. Reduced FA in the pyramidal tracts in ALS was associated with poor prognosis and FA reduction follows disease progression [116]. DTI can also be used for segmentation of white matter tracts, particularly the CST and corticobulbar tract (CBT) (Fig. 14.19), which may enable differentiation of clinical subtypes of ALS. For instance, FA values along the corticobulbar tract of bulbar-onset type are significantly lower than that of limb-onset type (Fig. 14.19) [110].

14.12 Huntington Disease (HD)

HD is an autosomal dominant disorder characterized by motor, cognitive, and behavioral disturbances. Age of diagnosis varies inversely with the expanded number of polyglutamine (cytosine-adenine-guanine or CAG) repeats in the huntingtin gene. Anatomically, HD primarily affects striatal neurons, with bilateral caudate atrophy being the most consistent imaging finding. Motor onset usually occurs in midlife, with a duration of 15–20 years after diagnosis. Striatal volume loss is present years before clinical diagnosis; however, white matter degradation is also prevalent and has been investigated as putative biomarker of the neurodegeneration. Increases in mean diffusivity (MD) and radial diffusivity (RD) in HD relative to controls were seen in inferior and lateral prefrontal cortex regions, which were seen at the prodromal stage of HD and tracked with baseline disease progression [117]. DTI metrics in selected tracts connecting the primary motor, primary somato-sensory, and premotor areas of the cortex with the subcortical caudate and putamen also suggested white matter degeneration, which were present up to a decade before predicted HD diagnosis [118]. Over a 2-year follow-up period, volumetric MRI was more sensitive to striatal degeneration in early symptomatic HD than DWI [119].

14.13 Secondary Neuronal Degeneration (Wallerian, Transneuronal, and Retrograde Degeneration)

There are three major types of secondary neuronal degenerations: (1) Wallerian degeneration (antegrade), (2) transneuronal/trans-synaptic degeneration (antegrade or retrograde), and (3) retrograde degeneration (Fig. 14.20) [120]. Wallerian degeneration is an antegrade degeneration of the axons and myelin sheath resulting from injury of the proximal portion of the axons or cell bodies. It is most commonly recognized in the corticospinal tract secondary to middle cerebral artery infarction. Wallerian degeneration can also be seen in corticobulbar and corticopontine tracts, the corpus callosum, and middle cerebral peduncles [121]. Energy depletion in layer 5 neurons may lead to failure of ion channel activity in the axolemma [122]. This results in axonal swelling followed by disintegration of the intra-axonal organelles. This in turn is followed by collapse of the myelin sheath and ensuing gliosis. DW imaging shows the acute phase of Wallerian degeneration as hyperintense signal associated with decreased ADC, presumably representing axonal and reactive astrocytic swelling [123, 124] (Fig. 14.21). DW high signals can be observed after more than 24 h following the associated territorial infarction [125]. In DTI, FA is reduced in the corticospinal tract, and may correlate with

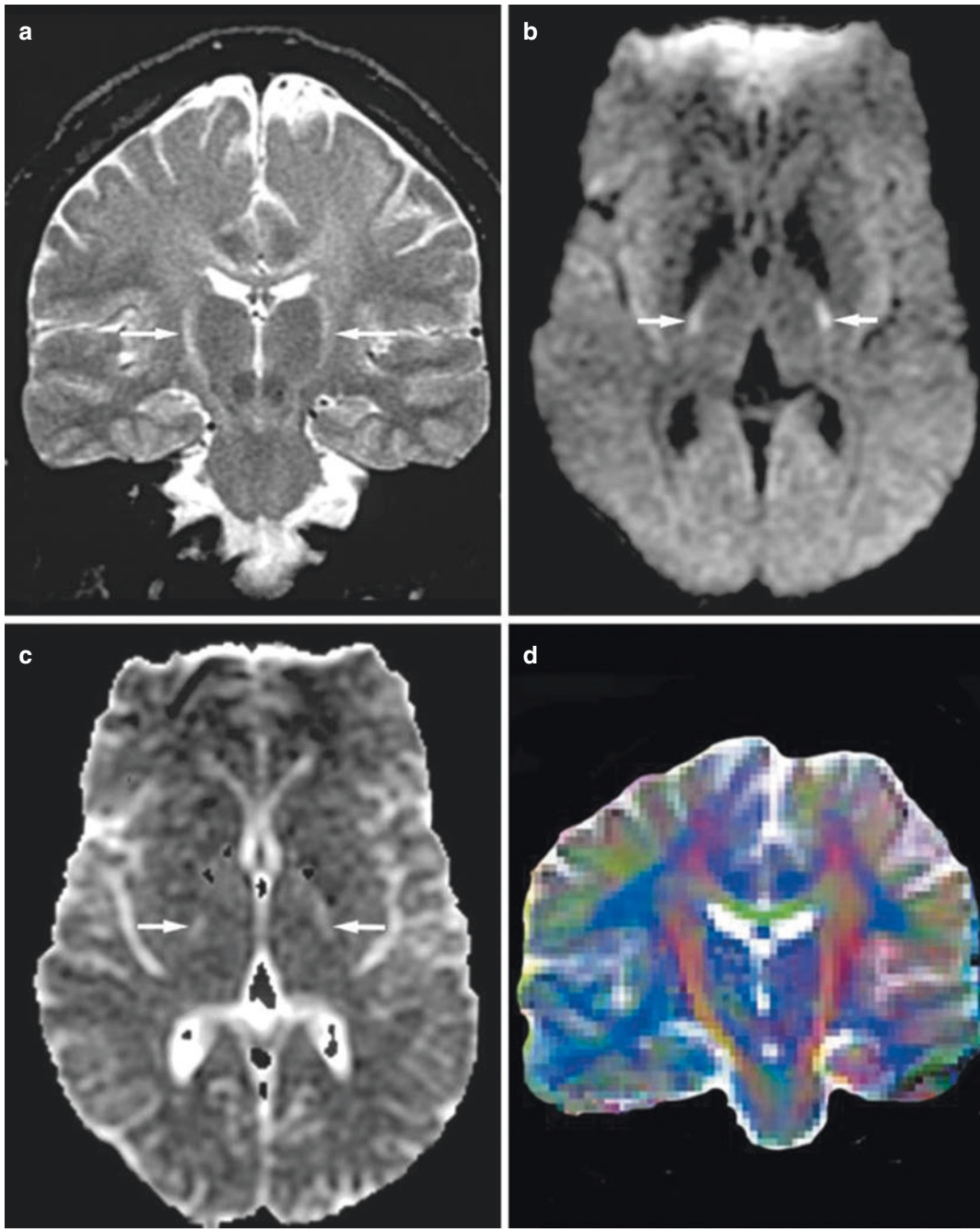
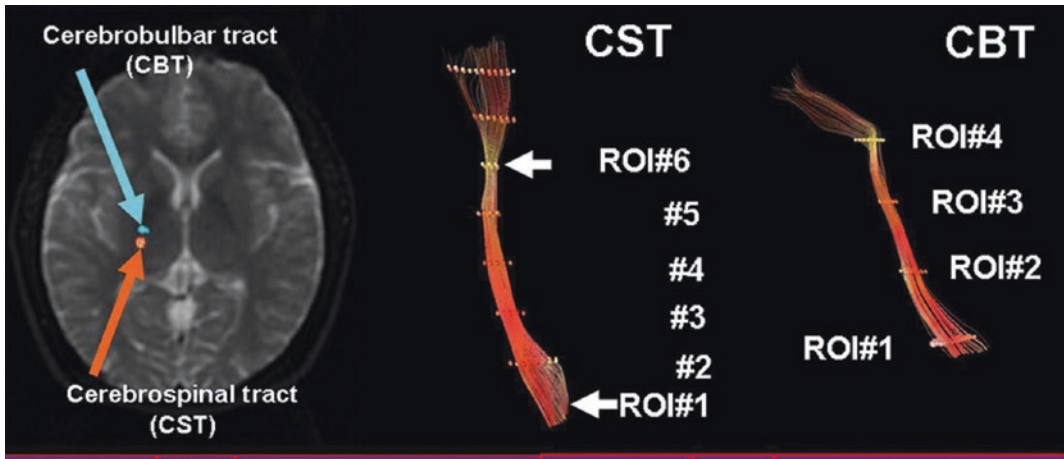


Fig. 14.18 Amyotrophic lateral sclerosis in a 27-year-old man with progressive weakness and dysphagia. (**a**) Coronal spin-echo T2-weighted image shows bilateral symmetrical hyperintensity along the corticospinal tract (*arrows*), extending into the white matter of the motor area. (**b**) DW image shows mild hyperintensity in bilateral corticospinal tracts. (**c**) ADC is increased (*arrows*). Hyperintensity and distortion in the frontal region are due to susceptibility artifact from air in the frontal sinuses. (**d**) Coronal diffusion tensor image with color mapping reveals decreased anisotropy along bilateral corticospinal tracts



DTT-CST	FA	p	DTT-CBT	FA	p
Limb-onset	0.594	p<0.05 (vs Normal)	Limb-onset	0.558	p<0.01 (vs Bulbar)
Bulbar-onset	0.574	p<0.01 (vs Normal)	Bulbar-onset	0.509	p<0.01 (vs Normal, vs Limb)
Normal	0.629		Normal	0.561	

Fig. 14.19 Tract-specific analysis of the corticospinal and corticobulbar tracts in amyotrophic lateral sclerosis. (Courtesy of Aoki S. MD, The University of Tokyo, Japan)

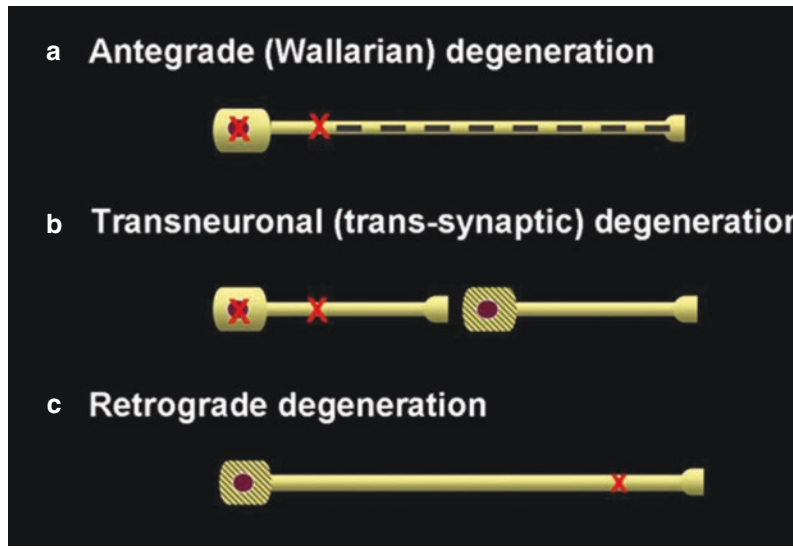


Fig. 14.20 Three major types of secondary degenerations. (**a**) Wallerian degeneration; an antegrade degeneration of the axons and myelin sheath resulting from injury of the proximal portion of the axons or cell bodies. (**b**) Transneuronal/trans-synaptic degeneration (antegrade type); a degeneration of the distal neuron via the synapse resulting from injury of the proximal portion of the axons or cell bodies. (**c**) Retrograde degeneration; a degeneration of the proximal neuron resulting from injury of the distal portion of the axons

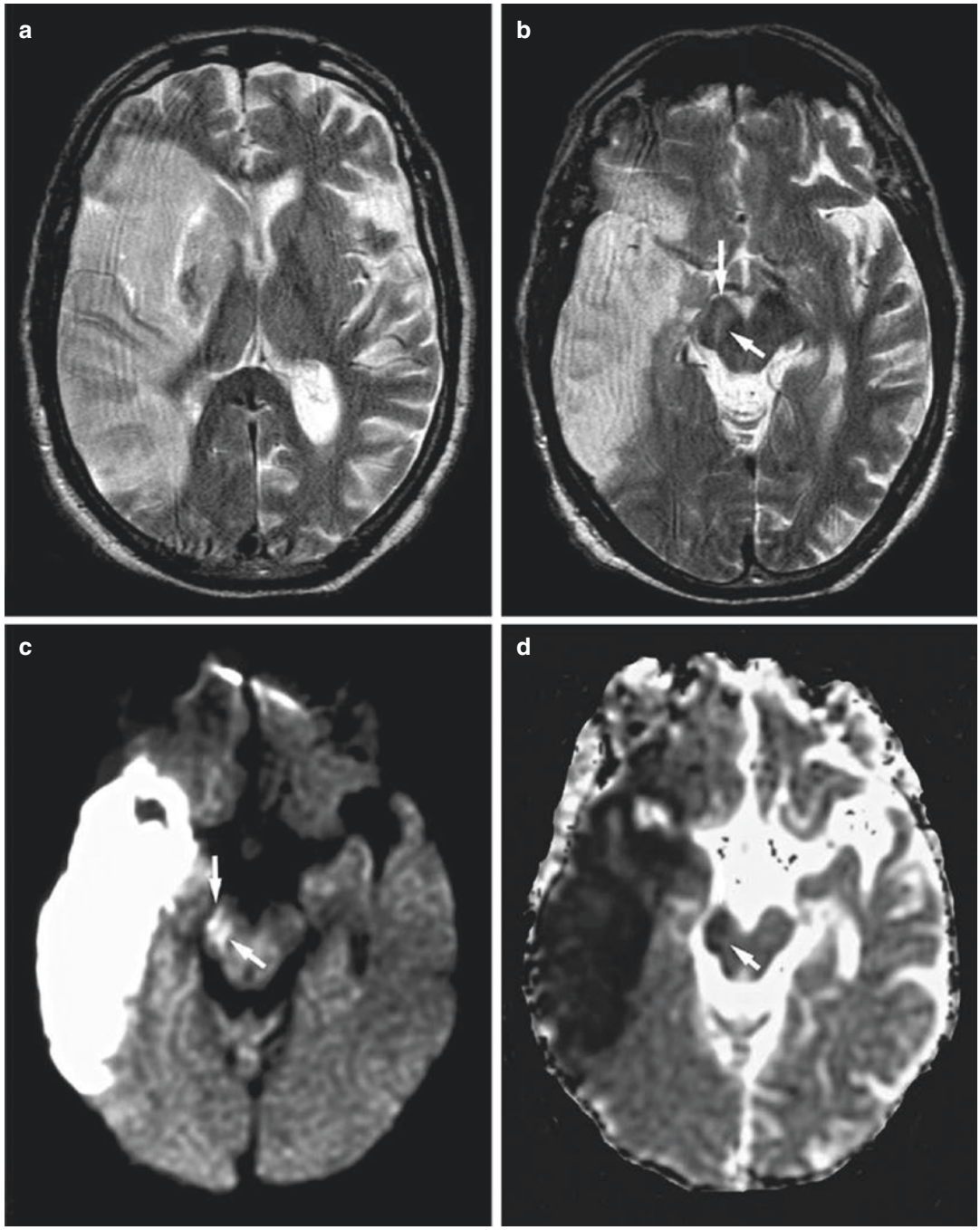


Fig. 14.21 Wallerian and transneuronal degeneration (acute phase) in a 76-year-old man with a large infarct in the right middle cerebral artery (MCA) territory (6 days after onset). (**a**) T2-weighted image shows a right MCA infarct as hyperintense, including the left putamen. (**b**) T2-weighted image at the level of the midbrain reveals a slightly hyperintense lesion in the right cerebral peduncle including the substantia nigra (*arrows*), as well as a right MCA infarct in the temporal area. (**c**) DW image shows hyperintensity in the T2 hyperintense foci seen in (**b**) (*arrows*). (**d**) ADC is decreased involving both the right cerebral peduncle and the right substantia nigra (*arrow*)

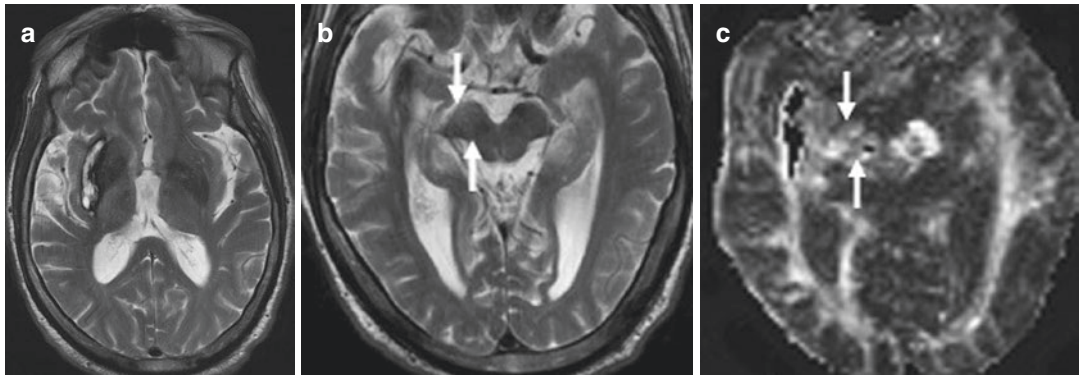


Fig. 14.22 Wallerian and transneuronal degeneration in a 78-year-old woman with right chronic putaminal hemorrhage. (**a**) T2-weighted image shows a right old putaminal hemorrhage as hypointense. (**b**) T2-weighted image at the level of the midbrain reveals mild hyperintense lesion in the right cerebral peduncle, including the substantia nigra (*arrows*). (**c**) FA map shows decreased anisotropy in the right cerebral peduncle (*arrows*)

impairment of motor function [126, 127] (Fig. 14.19). DT imaging is more sensitive than DW imaging in detecting chronic Wallerian degeneration [128].

Transneuronal (trans-synaptic) degeneration in the substantia nigra can occur secondary to striatal stroke [129]. This occurs along fiber connections originating in the caudate and putamen projecting over the substantia nigra (striatonigral pathway) [130]. Loss of inhibitory GABAergic output from the ischemic lesion can induce a postsynaptic long-term potentiation or a continuous excitatory state in the substantia nigra, resulting in neuronal swelling and cell death [131]. DW imaging shows hyperintensity associated with decreased ADC in the substantia nigra (Figs. 14.21 and 14.22) [132]. The decreased ADC of these lesions is thought to represent cellular edema of astrocytes or neurons in the substantia nigra. Diffusion abnormalities in the striatum or thalamus secondary to external capsular hemorrhage have also been reported, which are presumably related to antegrade transneuronal degeneration of the striatum (cortico-striatal fibers) and retrograde transneuronal degeneration of the thalamus (thalamostriate fibers) (Fig. 14.22) [133].

A distinct type of transneuronal degeneration relevant in neuroimaging is hypertrophic olivary degeneration (HOD). HOD ensues after damage to the dentato-rubro-olivary pathway, also known as the Guillain-Mollaret triangle. It results in palatal or oculopalatal myoclonus and cerebellar dysfunction [134]. HOD is a unique type of degeneration in that the degenerating olivary nuclei become transiently hypertrophic rather than atrophic and T2 hyperintense (Fig. 14.23). Interestingly, over 40% of HOD patients may not present an MRI-detectable lesion in the Guillain-Mollaret triangle [135].

Retrograde thalamic degeneration is usually seen in anterior and dorsomedial nuclei secondary to ipsilateral large infarction or hemorrhage. It is thought to be a retrograde degeneration through the thalamo-cortical pathways [136, 137]. DW imaging shows hyperintensity in the thalamic nuclei (Fig. 14.24).

14.14 Treatment Section: Treatment of Dementia

Juana Nicoll Capizzano

Introduction: New advances in the understanding of the pathophysiology of dementia illnesses have changed the management of patients with these disorders. The mainstay of management is still symptomatic; however, since there are no disease-modifying treatments currently available for any of the neurodegenerative dementias. However, it has been estimated that approximately 35% of AD

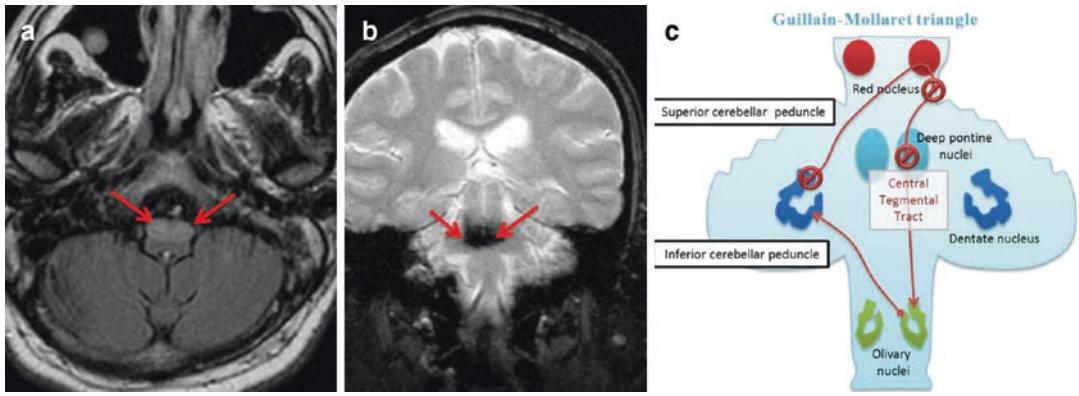


Fig. 14.23 (**a**) Hypertrophic olivary degeneration in patient with pontine hematoma (**b**). (**c**) Guillain-Mollaret triangle: Injury to the dentate nucleus, superior cerebellar peduncle, or central tegmental tract will result in transneuronal hypertrophic olivary degeneration

risk is modifiable with early life education and mid and late life control of vascular risk factors having a significant protective effect against late-life dementia [138]. The future promises disease-specific and, hopefully, disease-modifying treatments. Currently, the first step in dementia management is an accurate diagnosis of the type of dementia.

14.14.1 Alzheimer's Disease (AD)

It is the most prevalent neurodegenerative disease of aging, and it affects over 26 million people worldwide with this number continuously increasing [1, 139, 140]. The USA Food and Drug Administration (FDA) has approved five drugs for treatment of AD (Table 14.1). Three of these drugs are cholinesterase inhibitors, one is an N-Methyl-D-aspartate (NMDA) antagonist, and one is a combination of these two mechanisms. Additionally, addressing the treatment of behavioral and sleep problems is an important aspect of the care of patients with dementia.

Cholinesterase Inhibitors (ACHEIs): Patients with AD have reduced cerebral content of choline acetyl-transferase, which leads to a decrease in acetylcholine synthesis and impaired cortical cholinergic function. Cholinesterase inhibitors increase cholinergic transmission by inhibiting cholinesterase at the synaptic cleft. Evidence suggests that ACHEIs moderately improve cognitive and global function status of mild to moderate AD and DLB patients [141]. However, the efficacy wanes with long-term treatment due to side effects such as weight loss, diarrhea, and syncope [141]. On the other hand, ACHEIs may worsen behavioral symptoms in frontotemporal lobar degeneration (FTLD) [142].

N-methyl-D-aspartate (NMDA) receptor antagonists: Memantine blocks over-excited NMDA glutamate receptors, thereby inhibiting excitotoxicity [143]. Memantine alone or in combination with ACHEIs (Namzaric) has been approved for treatment of moderate to severe AD patients [144]. It has not been shown to be of benefit in mild AD. There is some evidence that it may be effective in vascular dementia and LBD/PDD [138].

Nonpharmacologic Therapy and Supportive Care: Non-pharmacologic interventions like diet, exercise, cognitive training, sleep hygiene, and vitamin supplementation have protective effects against cognitive decline and have been studied in AD prevention trials. The most promising dietary intervention has been the Mediterranean diet rich in fruits and vegetables, combined with olive oil and fish. The Three-City (3C) study suggested that participants who adhered to the Mediterranean diet had a slower rate of decline on the mini-mental status examination (MMSE) but not the other cognitive tests [145]. Furthermore, it has

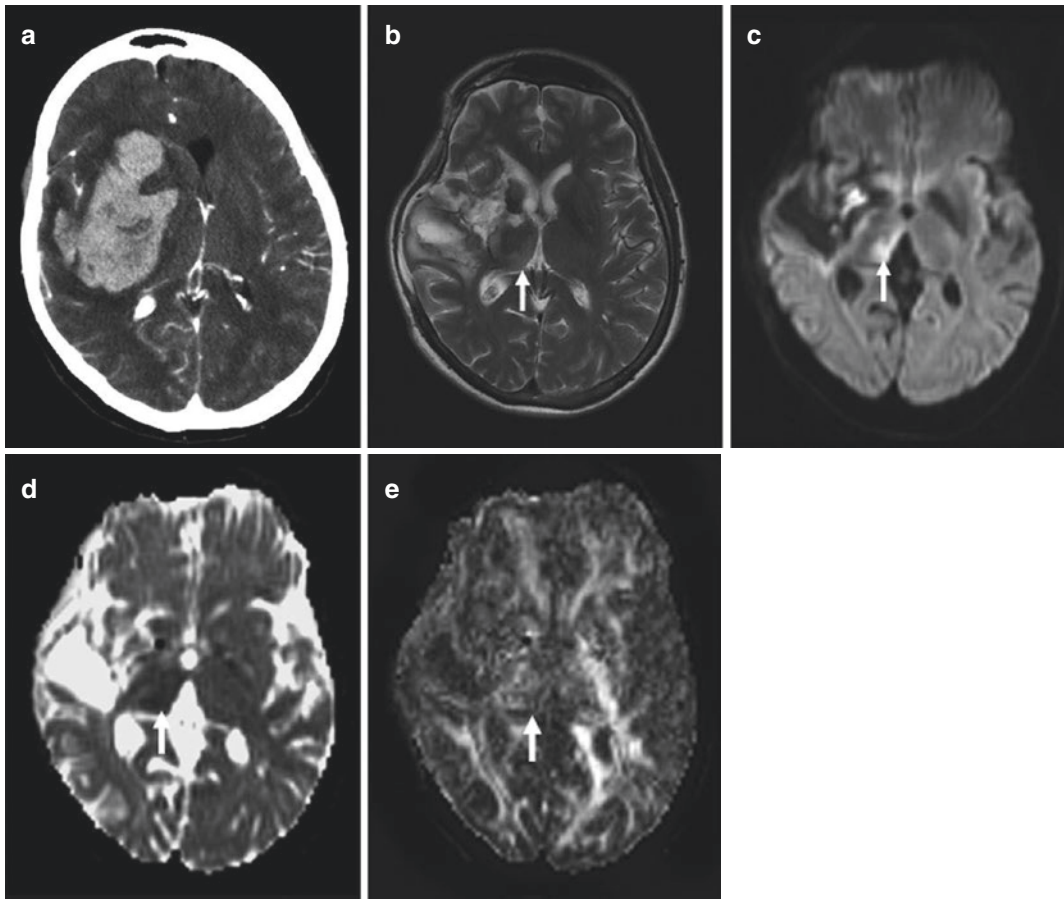


Fig. 14.24 Retrograde degeneration in the dorsomedial thalamus in a 56-year-old woman with right large putaminal hemorrhage. (**a**) Postcontrast CT shows a large hematoma in the right putamen extending into the frontotemporal region with edema and a mass effect. (**b**) The 2-month follow-up T2-weighted image shows a high signal intensity in the dorsomedial thalamus (*arrow*). Right craniectomy and extensive encephalomalacia are also noted. (**c**, **d**) DW image shows a hyperintense lesion with decreased ADC in the right dorsomedial thalamus (*arrow*). (**e**) FA map shows decreased anisotropy in the right internal capsule and dorsomedial thalamus (*arrow*). (Courtesy of Lee HK, MD, The University of Iowa Hospitals and Clinics, USA)

Table 14.1 Current US Food and Drug Administration-Approved Drugs for treating AD

Drug name	Trade name	Mechanism of action	Indication	Approval year
Donepezil	Aricept	Cholinesterase Inhibitor	Mild, moderate, and severe AD	1996
Rivastigmine	Exelon	Cholinesterase Inhibitor	Mild to moderate AD	2006
Galantamine	Razadyne	Cholinesterase Inhibitor	Mild to moderate AD	2001
Memantine	Namenda	NMDA antagonist	Moderate to severe AD	2003
Memantine plus Donepezil	Namzaric	NMDA antagonist and cholinesterase inhibitor	Moderate to severe AD	2014

also been shown that the Mediterranean Dietary Approach to Systolic Hypertension (DASH) intervention for neurodegenerative delay (MIND) diet may reduce the risk of Alzheimer's by up to 50%, and the protective effects persist until later time even when diet recommendations were not followed rigorously [146, 147].

Several studies have demonstrated that formal exercise programs may improve physical functioning and at least slow the progression of functional decline in patients with AD; however, current evidence is insufficient to provide detailed recommendations regarding specific physical exercise linked to AD prevention, e.g., type, frequency, intensity, and duration of exercise [148]. Overall, it is indicated that physical activities combined with social and cognitive stimulation or diet modification may be more beneficial at reducing risk of AD [148].

In the past decade more attention has been brought to the use of supplements such as vitamin E, Gingko biloba, and omega-3 fatty acids for AD prevention. Based on recent systematic reviews, there is no evidence suggesting any beneficial effects of vitamin E on preventing MCI conversion into AD or improving cognitive function of MCI or AD patients [149]. However, results from a single study of combined vitamin E and memantine therapy in AD suggest that vitamin E may delay functional decline in these patients by 19% per year versus placebo [150, 151].

Cognitive interventions hold promise for the mitigation of cognitive symptoms in dementias. Strategies include cognitive stimulation and neurorehabilitation. However, the evidence for their efficacy is lacking. Finally, it is paramount that caregivers be taught about what to expect from the course of the disease, the underlying causes of behavior changes, and be trained on how to problem solve situations with regard to dementia [138].

14.14.2 Vascular Dementia (VaD)

Vascular cognitive impairment (VCI) is defined as cognitive impairment associated with clinical stroke or subclinical vascular brain injury and ranges from mild cognitive impairment (MCI) to its most severe form, vascular dementia (VaD) [152]. VCI is the second most common type of dementia after AD. VCI has received significant attention recently as a potentially preventable and treatable cause of cognitive impairment [153, 154].

Acetylcholinesterase inhibitors are believed to improve cognition in patients with AD by increasing the availability of acetylcholine in the synaptic cleft. There is also evidence that these medications increase cerebral blood flow [152, 155, 156]. Therefore, these drugs are considered as a potential treatment option in patients with VCI. However, in clinical trials, dose–response effects to acetylcholinesterase inhibitors in VCI have not been consistent. Moreover, no definitive benefit is seen in patients with VaD in global functioning when treated, thus, no acetylcholinesterase inhibitors has received FDA approval for use in VaD.

Herbal Medicines: There is a long history of herbal medicine used to boost memory and cognitive functions and to manage behavioral and psychological symptoms associated with neurodegenerative or vascular dementia. Some of the most commonly used and studied herbs include Ginkgo biloba, Huperzia serrata, Curcuma longa, Panax notoginseng, and Bacopa nonnieri. Gingko Biloba is one of the most studied medicinal herbs. Ginkgo leaf extract is widely used for aging-related memory disorders in many European and Asian countries. The principal constituents of ginkgo include flavonol glycosides and terpenoids [157]. Preclinical studies suggest that ginkgo decreases oxygen radical discharge and proinflammatory functions of macrophages (antioxidant and anti-inflammatory), reduces corticosteroid production (antianxiety), and increases glucose uptake and utilization and adenosine triphosphate (ATP) production [158].

In animal studies, the effects of ginkgo leaf extracts on neuroprotection and cognitive dysfunction have been demonstrated in various cerebral ischemia models in rats, mice, and gerbils [159, 160]. In healthy young adults, ginkgo treatment has been shown to improve speed of processing, working memory, executive function, and cognition [161]. The evidence to support the use of gingko for dementia remains controversial. Although clinical studies failed to show a significant difference between ginkgo and placebo in dementia groups [162], there are

potentially beneficial effects for dementia when it is administered at doses greater than 200 mg/day for at least 5 months [163]. Given the lower quality of the evidence, further rigorously designed, multicenter-based, large-scale RCTs are warranted.

14.14.3 Dementia with Lewy Bodies (DLB)

DLB is characterized by dementia, cognitive fluctuations, visual hallucinations, parkinsonism, and rapid eye movement (REM) sleep behavior disorder [36]. It was first described as separate disease entity by Kosaka and colleagues [164]. DLB has a marked clinicopathologic overlap with Parkinson's disease dementia (PDD) posing challenges to distinguish between DLB and PDD in clinical practice.

14.14.3.1 Symptomatic Treatment Options for DLB

- **Dementia, visual hallucinations, and other neuropsychiatric disturbances**: Cognitive impairment is usually the initial symptom of DLB, and cognition can exhibit a more rapid decline as compared with AD. Cholinesterase inhibitors (AChEIs) rivastigmine and donepezil are the first-line treatment recommended for cognitive disturbances in DLB [165]. However, despite the cholinergic hypothesis, cholinesterase inhibitor drugs have demonstrated limited effectiveness in clinical practice.
- **Neuropsychiatric symptoms**: These are associated with the higher distress that DLB caregivers experience, and they include visual hallucinations, delusions, depression, apathy, anxiety, psychomotor excitement, and agitation. Neuropsychiatric symptoms are attributed to dysfunctional, decreased serotonergic, and cholinergic neurotransmission [166]. None of the AChEIs has been found to be better than other because there are no head-to-head trials comparing their efficacy in DLB. Japanese authors described in several reports the complete disappearance of visual hallucinations after treatment with donepezil, suggesting a dose-dependent effect and recommending donepezil as the first-choice drug for the treatment of DLB-related psychotic symptoms [167].
- The use of antipsychotics for the acute management of substantial behavioral disturbances, delusions, or visual hallucinations comes with significant mortality risks in patients with dementia, and they should be avoided whenever possible, given the increased risk of a serious neuroleptic sensitivity reaction [168]. Low-dose quetiapine may be relatively safer that other antipsychotics and is widely used. In alignment with general advice on depression in dementia, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and mirtazapine are options in DLB with treatment guided by individual patient tolerability and response.
- **Motor symptoms**: Parkinsonism is often less responsive to dopaminergic treatments in DLB than in Parkinson's disease, and their use may be associated with an increased risk of psychosis. Levodopa is generally well-tolerated in modest doses by DLB patients, without producing neuropsychiatric side effects [168]. Patients at risk of falling may benefit from safety assessment as well as bone mineral density screening, and assessment of vitamin D status to manage risk of fractures. Sleep disorders can be managed with melatonin as a possible safe option. Clonazepam carries a risk of worsening cognition and gait impairment and should be avoided [169].

14.14.4 Parkinson's Disease (PD)

Is the second most common neurodegenerative disorder after AD affecting more than 6 million people worldwide [170]. Management remains complicated over the course of the disease and should be individualized based on the patient's quality of life at each stage of the disease. Dopaminergic medica-

Table 14.2 Current US Food and Drug Administration-Approved Drugs for treating PD

Agent	Mechanism of action	Side effects	Typical dose	Level of evidence
Levodopa (with carbidopa or benserazide)[a] (Sinemet, Levocarb, Prolopa)	Metabolizes to dopamine	Nausea, vomiting, constipation, psychosis, hallucinations, hypotension, and dyskinesias.	300–1200 mg (higher if tolerated)/day (Divided tid,qid,q3h,q2h)	**A**
Dopamine agonists (Ropinirole, Pramipezole and Rotigotine patch)	Directly stimulate dopamine receptors	As above, plus leg edema, reward-seeking behavior, daytime sleepiness, and sudden-onset sleep. Skin reactions with the rotigotine patch	Ropinirole: 3–24 mg/day (TID) Pramipexole: 1.5–4.5 mg/day (TID) Rotigotine: 4–8 mg/24 h (patch)	**A**
Catechol-O-methyltransferase (COMT) inhibitors (Entacapone)	Blocks peripheral COMT activity	Related to increased levodopa delivery: diarrhea, urine discoloration.	200 mg pill, up to 8 times/day (given with each dose of levodopa)	**A**
Monoamine Oxidase (MAO) Inhibitors (Selegiline, Rasagiline)	Blocks MAO-B to reduce metabolism of dopamine (central and peripheral)	Nausea, hypotension, confusion, hallucinations.	Rasagline: 0.5–1 mg/day (od) Selegiline: 5–10 mg/day (BID) early in the day.	**A**
Amantadine	Blocks NMDA and acetylcholine receptors.	Confusion, hallucinations, leg edema, rash (livedo reticularis)	100 mg od to 100 mg (TID)	**C**
Anticholinergics (e.g., trihexyphenidyl)	Blocks acetylcholine receptors	Dry eyes and mouth urinary retention, confusion, worsening of glaucoma	Trihexiphenadyl: 1–6 mg/day (TID)	**U**

Levels of evidence are derived from the American Academy of Neurology recommendations: A = established effective, B = probably effective, C = possibly effective, U = date inadequate or conflicting

[a]Levodopa should be taken 1 h prior to, or 2 h after, meals containing protein, to improve absorption. Sinemet CR (controlled release 100/25 and 200/50 mg) cannot be used to reduce frequency of immediate-release levodopa administration

tions are the mainstay of symptomatic therapy for motor symptoms. The mechanism of action, starting and target doses and adverse effects are summarized in Table 14.2 [171].

Anticholinergics, such as trihexyphenidyl, may be used in patients with early-onset Parkinson disease and severe tremor, but not as a first choice owing to limited efficacy and propensity of neuropsychiatric adverse effects. Recent data show that injections of botulinum toxin may effectively treat the tremor from of Parkinson disease [172].

Drugs that should be avoided in PD: Drugs that block dopamine receptors can result in parkinsonism or substantially worsen motor symptoms in patient with PD and may lead to neuroleptic malignant syndrome. These include neuroleptics such as haloperidol, thioridazine, chlorpromazine, promethazine, fluphenazine, risperidone, and olanzapine. Antiemetics such as prochlorperazine and metoclopramide, tetrabenazine and antihypertensives, such as methyldopa [173]. Meperidine should be avoided in those receiving monoamine oxidase B inhibitors [173].

Deep Brain Stimulation: Approved in 2002 as an adjunctive therapy for reducing motor fluctuation in advanced PD. The globus pallidus interna and the subthalamic nucleus are accepted targets for this procedure.

Good candidates are those patients with adequate response to dopaminergic therapy, presence of on–off fluctuations, age <70 years, and dyskinesia impairing quality of life and medication-resistant tremor. Poor candidates are those with severe dementia, severe autonomic dysfunction, poor dopaminergic response, atypical parkinsonism, unstable psychiatric disease or absence of a dedicated caregiver.

Patients should be considered for deep brain stimulation only if adequate trials of multiple medications for PD have been unsuccessful [174]. Although duration of therapy is not clearly established, patients who undergo deep brain stimulation may have sustained benefit for at least 10 years [174].

Levodopa-carbidopa intestinal gel: For patients who are not candidates for or decline deep brain stimulation, levodopa-carbidopa intestinal gel may be considered. This gel is pumped into the jejunum via a percutaneous tube insertion, recently approved for the treatment of motor fluctuations in PD [175]. Administration of the gel has been shown to result in faster absorptions, comparable bioavailability and reduced intra-subject variability in levodopa concentrations compared with oral levodopa-carbidopa [176].

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