# Primary Grey Matter Loss

# 5

## Contents



## 5.1 Introduction: Primary Grey Matter Loss

Many dementias are characterised by grey matter (GM) abnormalities; these are usually, but not exclusively, atrophy. AD is the most prevalent and the prototypic cortical GM dementia. GM atrophy reflects a loss of neurons irrespective of the underlying protein defect (amyloid, tau, alpha-synuclein); atrophy may be generalised or focal, and the pattern of atrophy may be diagnostic in itself.

The current chapter focuses on disorders principally affecting GM, encompassing, besides AD, the growing class of frontotemporal lobar degeneration syndromes, including FTD and PPA, CBD and PSP, as well as PD with dementia as in DLB, Huntington's disease and many less common diseases. A special chapter is dedicated to the prion diseases that typically affect the more basal grey matter structures as well.


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## 5.2 Alzheimer's Disease

**Synonyms**

Senile Dementia of Alzheimer type; Senile Dementia; Presenile Dementia; Alzheimer's disease (AD); Degenerative Dementia

### 5.2.1 History

The disease is named after Aloïs Alzheimer, who presented his observations on a case of a 51-year-old woman in 1906. In her brain, Alzheimer found the hallmarks of the disease that now bears his name, the senile plaques and neurofibrillary tangles – findings that had been described before, but not in the context of a progressive dementia. The disease that was named after him by Kraepelin in 1914 remained a rare disorder until large autopsy series carried out in the USA and UK found that the same changes were present in elderly individuals that presented with cognitive decline. Subsequently, Alzheimer's disease became synonymous for any type of dementia occurring at any age. It was not until 1984 that a work group under the auspices of the NINCDS formulated the first clinical criteria.

### 5.2.2 Histopathology

The diagnosis of AD is ultimately made by pathological examination of the brain (at autopsy or by brain biopsy in exceptional cases). Macroscopic examination reveals gross atrophy, also reflected by a severely decreased brain weight (usually below 1,000 g), affecting mostly the temporo-parietal regions (Fig. 5.1), sometimes however, quite prominent at the frontal poles. The characteristic lesions at the microscopic level are extracellular neuritic plaques, consisting of a core composed of beta amyloid (abeta), and intracellular neurofibrillary tangles (NFT) consisting of hyperphosphorylated tau-protein (Figs. 5.2–5.4).

On a semantic level, the term 'senile plaques' means amyloid plaques for US scientists, but neuritic plaques for European neuropathologists, and probably also for Aloïs Alzheimer himself, when dealing with silver staining of brain tissue sections. Therefore, senile plaques can be considered as 'neuritic plaques', that is amyloid plaques surrounded by degenerating neurites filled with tau pathology. This is why neuritic plaques (amyloid + tau) are the best histological markers of AD. Amyloid plaques are found in both non-demented and demented patients, while neuritic (senile) plaques are only found in demented patients. The staging system developed by Braak and Braak (see Fig. 5.5) describes the extent, location and the presumed sequence of accumulating neurofibrillary tangle pathology, which in AD is thought to start in the transentorhinal and entorhinal areas, before spreading to the hippocampus, the association cortices, and the rest of the cortex.

Current histological criteria for the diagnosis of AD are based on the density of neuritic plaques and NFTs in the neocortex and limbic areas. Various sets of histopathological criteria exist (NIA-Reagan, CERAD) that may not be in agreement. While histopathological diagnosis is still considered the gold standard, considerable discrepancies between pathological diagnoses at post-mortem and the clinical diagnoses during lifetime exist. A prospective, population-based study on the prevalence of AD in people over 85 years found

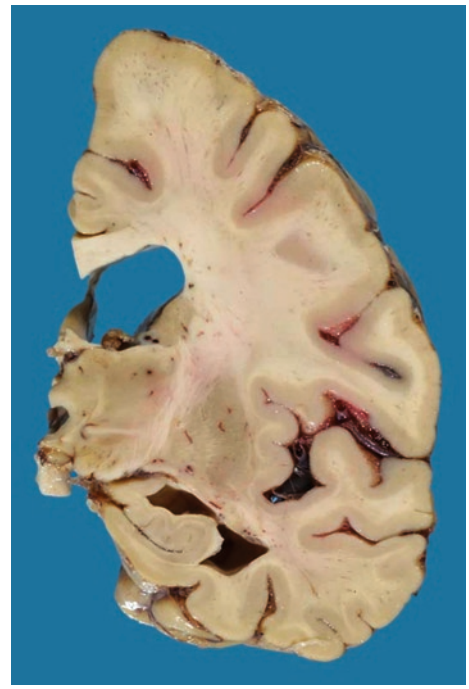


**Fig. 5.1** Coronal cut of the brain of a patient with AD. Note mild ventricular dilatation including the inferior horn, secondary to hippocampal atrophy

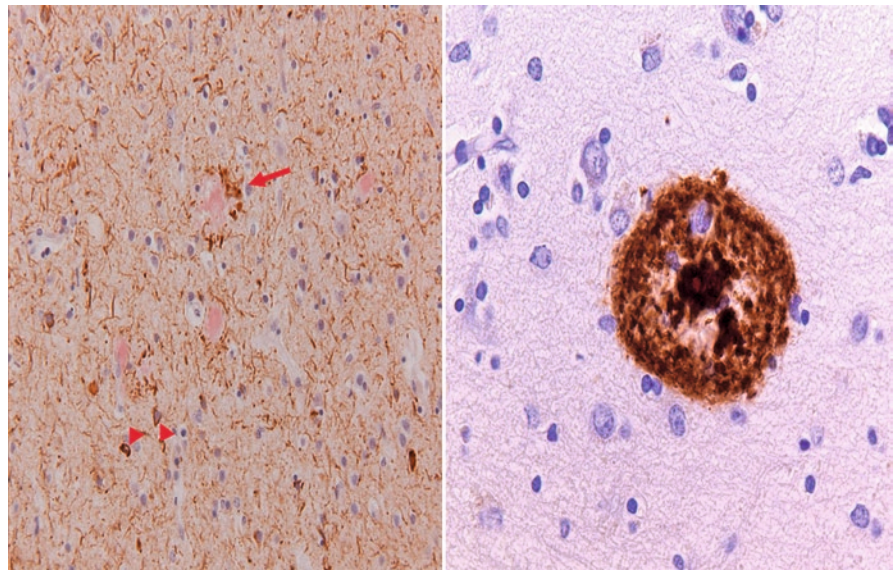


**Fig. 5.2** Histopathology in cortex of an AD patient. *Left* image stained with tau (*brown*), Congo-red (*red*) and haematoxylin blue. The *long arrow* points at a neuritic plaque with a red nucleus of amyloid with a tau-positive corona; *arrowheads* point at tangles. Magnification on the *right* shows the amyloid core with a dense corona of tau-filled neurites

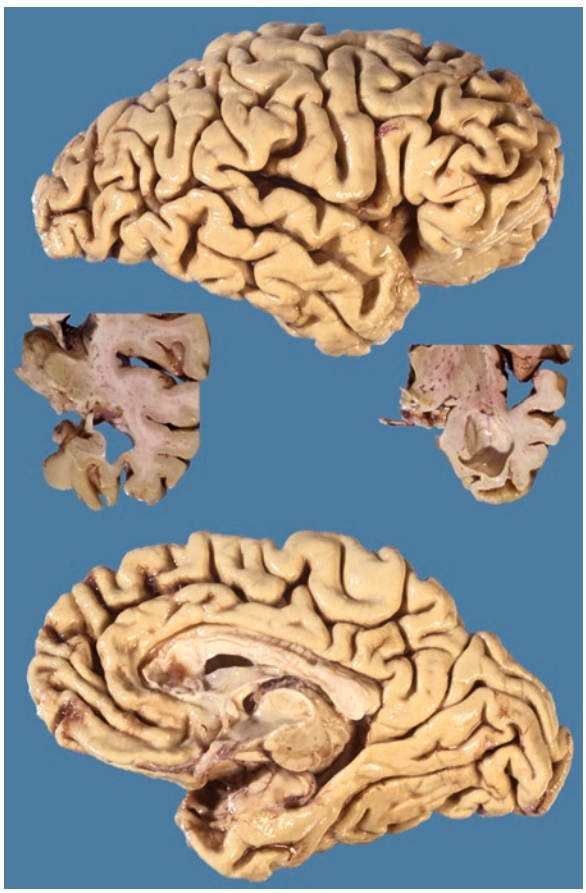


**Fig. 5.3** Gross specimen of familial AD patient. Lateral and medial view showing prominent temporal as well as parietal atrophy with widening of the Sylvian fissure. Note the marked mediotemporal atrophy on the inserts

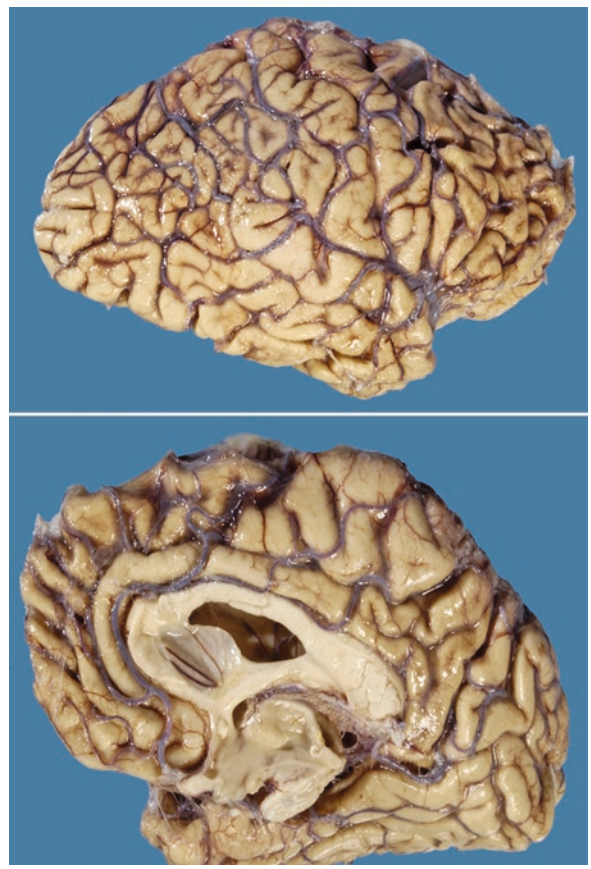


**Fig. 5.4** Atypical distribution of atrophy in AD. Macroscopic image of an AD patient showing remarkable frontal lobe atrophy

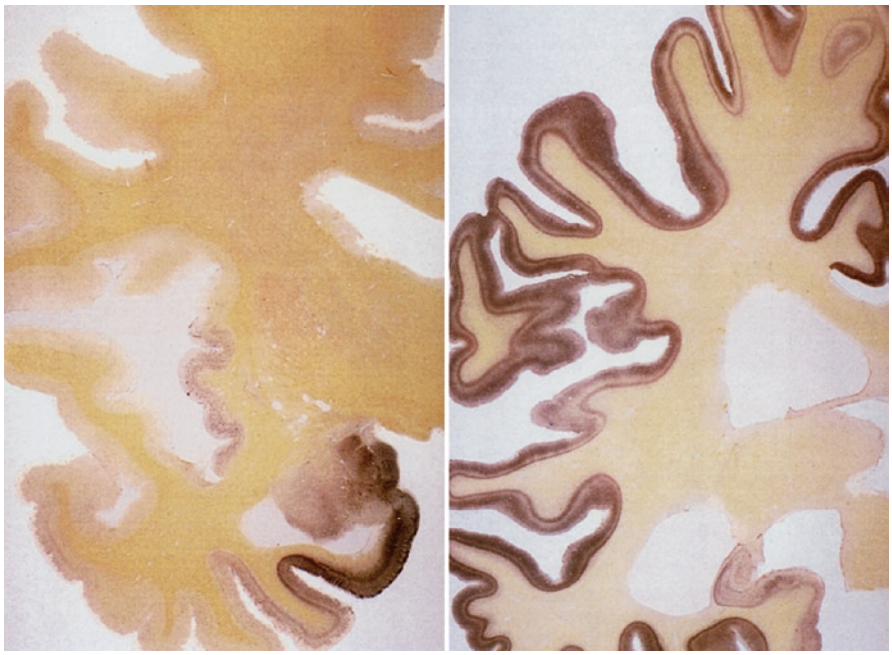


**Fig. 5.5** Braak stages of cortical spreading in AD. Neurofibrillary tangles start to accumulate in the entorhinal region and spread from there to the amygdala, hippocampus, and finally involves virtually every subdivision of the cerebral cortex. The anatomical specimen on the *left* shows stage IV, in which destruction of the entorhinal area has spread into the amygdala, hippocampal formation and, in particular, from the transentorhinal region into the adjoining association areas of the temporal neocortex. At this stage the disease is becoming clinically manifest. The anatomical specimen on the *right* illustrates stage V–VI of the progress of Alzheimer's disease, with a high density of neurofibrillary changes in the entire cortex. This stage represents full-blown AD. (Courtesy of H. and E. Braak, Goethe University, Frankfurt/Main, Germany)

that 55% of the individuals who met the neuropathological criteria for AD were either not demented during life-time or classified as vascular dementia. Conversely, 35% of patients with clinical AD did not fulfil the pathological criteria. In spite of this, the prevailing theory regarding the origin of AD is reflected by the Amyloid cascade hypothesis, originally coined by Selkoe and Hardy (Fig. 5.6).

Amyloid pathology is not confined to AD, but is also found in other diseases, like Lewy body dementia and cerebral amyloid angiopathy. The majority of subjects with clinical, late-onset AD show co-existing vascular pathology at post-mortem and it is quite plausible that the two pathologies interact (e.g. vessel wall changes and hypo-perfusion accelerating AD); see also Sect. 6.7.

### 5.2.3 Genetics

The cause of AD is still not fully understood, except for the familial autosomal dominant inherited cases with early onset, associated with mutations in the amyloid precursor protein (APP) and presenilin genes (PSEN1 and PSEN2). However, the familial form of AD is extremely rare, with prevalence below 1%. The far more common, sporadic form of AD is genetically associated with the apolipoprotein E4 allele (APOEe4), although APOEe4 is neither necessary nor sufficient to cause AD. The APOEe4 allele increases the risk of the disease threefold in heterozygotes and by 10–15 times in homozygotes. Apart from genetic risk factors, the most important risk factor for AD is age. It is estimated that both the incidence and the prevalence double with every five year increase in age. Other risk factors for AD include female sex and vascular risk factors, such as diabetes, hypercholesterolemia and hypertension. Whether these vascular risk factors are causally related to the neuropathological process of AD or induce cerebrovascular damage that coincides with or adds to Alzheimer-type neuropathology remains to be established and are important issues with regard to potential preventive measures.

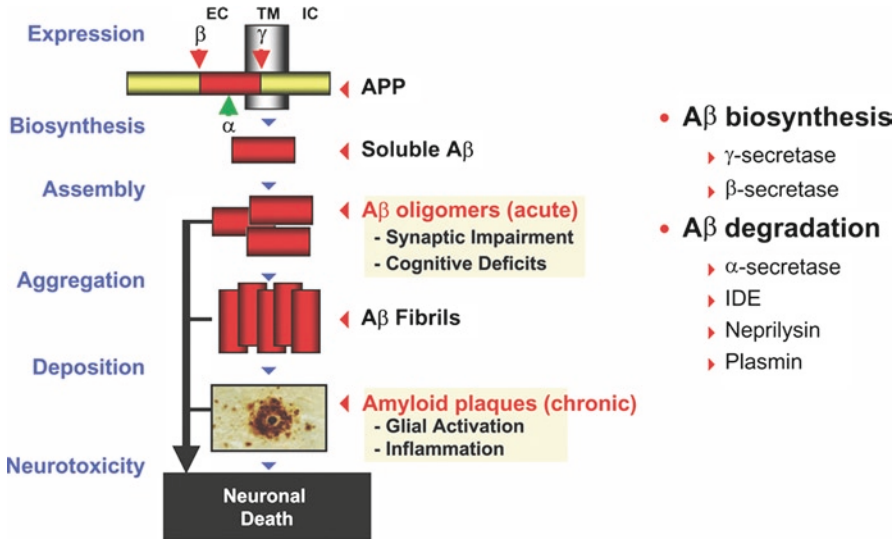



**Fig. 5.6** Amyloid cascade. Abnormal cleavage of APP leads to amyloid aggregation and plaque formation. (Reprinted with permission from Biochem Soc Trans 2005;33:553–558)

### 5.2.4 Clinical Presentation

Typically, AD is characterized by an insidious onset of cognitive decline, starting with deficits in episodic memory. Patients and their family complain, for example, of forgetting recent personal and family events, losing items around the house, and repetitive questioning. As the disease progresses, other deficits such as aphasia, apraxia, agnosia, visuo-spatial difficulties and executive dysfunction, arise gradually. In Fig. 5.7, a typical example of the clock drawing test is given. This test relies on visuospatial, praxis and executive abilities. Short of a full neuropsychological examination, a simple bed-side test called the "mini-metal state examination (MMSE)" can be used. Normal subjects score 27 or higher on the 30-point MMSE scale, although cut-off values are somewhat dependent on education.

Psychiatric and behavioural problems such as mood disorders, psychosis, agitation and sleep disorders occur more frequently as the disease progresses. The patient becomes increasingly dependent on others. Clinical diagnosis is made using criteria, of which the Mckhann criteria published in 1984 are the most widely validated and used. The criteria discern three categories of certainty: definite AD (established by post-mortem or

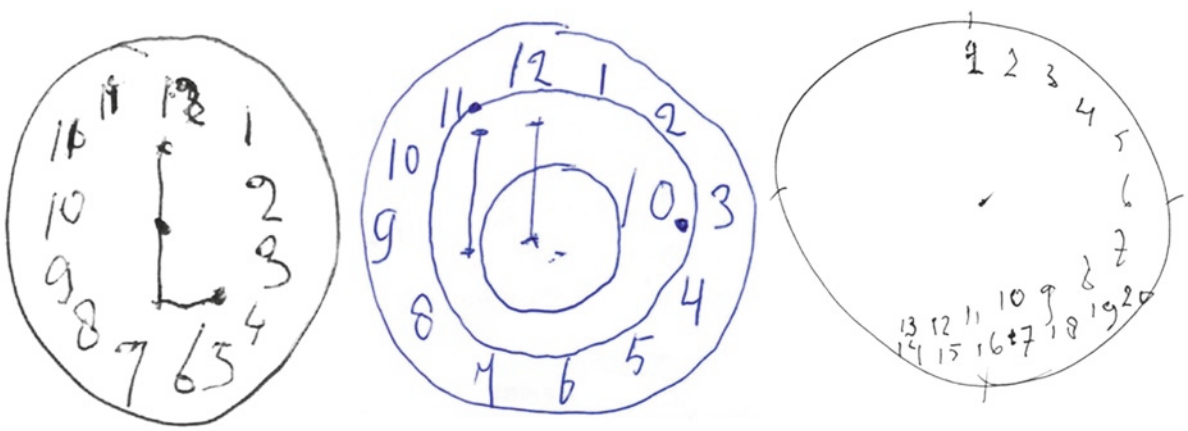


**Fig. 5.7** Clock drawings by patients with AD. Patient is asked to draw a clock and set the time for 10 min past 11 o'clock. Shown are three examples of different patients with various degrees of severity of visuospatial and executive functions. Note that none of the clocks has the hands placed correctly or at all

**Table 5.1** NINCDS-ADRDA criteria for probable AD

| |
|---|
| 1. Dementia established by clinical examination and confirmed by neuropsychological tests |
| 2. Deficits in two or more areas of cognition, including memory impairment |
| 3. Progressive worsening of memory and other cognitive functions |
| 4. No disturbances of consciousness |
| 5. Onset between ages 40 and 90 |
| 6. Absence of systemic disorders or other brain disease that in and of themselves could account for the progressive deficits in memory and cognition |

*Source:* McKahnn et al. Neurology 1984;34:939–944

biopsy), probable AD (Table 5.1) and possible AD (when there are other explanations for the cognitive syndrome that are as likely). The average survival in AD is typically about 8–13 years from the onset of symptoms.

Since the publication of the NINCDS-ADRDA criteria, the elucidation of the biological basis of AD has advanced greatly, allowing a better understanding of the disease process. The clinical phenotype of AD is no longer described in exclusionary terms, but can be characterized more definitively on a phenotypic basis. Distinctive markers of the disease are now recognized including structural brain changes on MRI with early and extensive involvement of the medial temporal lobe, functional neuroimaging changes on PET with hypometabolism or hypoperfusion in temporo-parietal areas, amyloid imaging with specific PET ligands and changes in CSF biomarkers. A driving force behind this emerging identity of AD has been the intense research interest in characterizing the earliest stages of AD that predate the crossing of the dementia threshold, defined by functional disability. From this, a need was felt to identify prodromal AD that must be distinguished within the broad and heterogeneous state of cognitive functioning that falls outside normal aging described by a wide range of terms including Age-Associated Memory Impairment, Age-Related Cognitive Decline, Age-Associated Cognitive Decline, Mild Cognitive Disorder, Mild Neurocognitive Disorder, Cognitively Impaired Not Demented, and Mild Cognitive Impairment (MCI).

#### 5.2.4.1 From MCI to Prodromal AD

This designation of MCI has been the most widely used diagnostic label referring to individuals who have subjective memory and/or cognitive symptoms accompanied by objective evidence of isolated memory and/or other cognitive impairment and whose activities of daily living are considered to be generally normal. Progression to clinically diagnosable dementia occurs at a higher rate from MCI than from normal (typically 10–15% per year – compared to rates of ~1% with normal ageing), but is clearly not the invariable clinical outcome at follow-up. A more refined definition of AD is then required, to reliably identify individuals with the disease at its earliest stages. A large group of EU–US investigators has formulated new criteria for this earliest stage of AD, starting from the presentation with a memory complaint in typical AD (see also Chap. 2) and adding biomarker information from MRI, PET or CSF or genetic confirmation. The proposed criteria are listed in Table 5.2.

**Table 5.2** Prodromal Alzheimer's disease criteria. (A plus one or more supportive features B, C, D, or E)

| |
|---|
| Core diagnostic criteria |
| A. Presence of an early and significant episodic memory impairment which includes the following features:<br>(i) Gradual and progressive change in memory function reported by patient or informant over more than 6 months<br>(ii) Objective evidence of significantly impaired episodic memory on testing: this generally consists of memory performance that does not improve significantly with cueing or recognition testing and after effective encoding of information has been previously controlled.<br>(iii) The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances. |
| Supportive features (B and/or C and/or D and/or E) |
| B. Presence of medial temporal lobe atrophy<br>Volume loss of hippocampus, entorhinal cortex, amygdala evidenced on MRI with:<br>• Qualitative ratings using visual scoring (referenced to well-characterized population with age norms) or quantitative volumetry of regions of interest (referenced to well-characterized population with age norms). |
| C. Abnormal CSF biomarkers:<br>• Decreased Aβ 1–42 and/or increased total tau and/or increased phospho-tau.<br>• Other well-validated markers to be discovered in the future. |
| D. Specific pattern in functional neuroimaging with PET:<br>• Reduced glucose metabolism in bilateral temporal parietal regions.<br>• Other well-validated ligands including those that foreseeably will emerge such as PiB or FDDNP. |
| E. Proven AD autosomal dominant mutation within the immediate family. |

*Source:* Dubois B et al. Lancet Neurol 2007;6:734–746

**Table 5.3** Atypical presentations of AD

- Posterior presentations of AD (includes 'posterior cortical atrophy'; 'biparietal AD' and 'visual variants')
  - Balint's like syndrome (optic ataxia, simultanagnosia, optic apraxia)
  - Visual disorientation and navigation problems
  - Aperceptive visual agnosia
  - Limb apraxia and a corticobasal syndrome
- Frontal presentations
  - Behavioural disturbances resembling FTD; apathy
- Language presentations
  - Fluent or non-fluent aphasia; logopenic variant

#### 5.2.4.2 Atypical Presentations of AD

Besides the typical neuropsychological profile of AD presenting with early memory deficits as mentioned above, there is evidence from clinico-pathological studies that AD patients may present with different neuropsychological profiles (Table 5.3). These atypical variants of AD suggest that the distribution of neuropathological changes (Fig. 5.4) rather than the nature of the disease are reflected in the clinical syndrome and that in clinical practice AD should be considered as diagnosis in a broad range of focal cognitive syndromes. Atypical presentations are more often seen in young onset AD patients (arbitrarily defined as before the age of 65) and in patients not carrying an APOE4 allele.

### 5.2.5 Differential Diagnosis of AD

When a patient fulfils clinical criteria as mentioned in the previous paragraph, there is still a chance that the patient has in fact a different underlying pathological substrate. Although this can never be ruled out completely in vivo, there are certain clinical features that render the diagnosis of AD less likely. In Table 5.4, these clinical features, or red flags, are listed, with the other diagnostic considerations listed along side.

In addition to the above, the differential diagnosis of early onset dementia is much wider than AD alone. In fact, in the young, AD and FTD have been reported to be equal in prevalence (see also Sect. 2.3). A careful and detailed history and the use of ancillary investigations are needed to disentangle the various underlying possible pathologies.

**Table 5.4** Clinical Red flags and alternative diagnostic considerations

| Red flag | Alternative diagnosis |
|---|---|
| Abrupt onset | VaD |
| Stepwise deterioration | VaD |
| Prominent behavioural changes | FTD, VaD |
| Profound apathy | FTD, VaD |
| Prominent aphasia | SD, PNFA, VaD |
| Progressive gait disorder | VaD, NPH |
| Prominent fluctuations in level of consciousness | Delirium due to infection, medications, or other causes |
| or cognitive abilities | DLB, Temporal lobe epilepsy, OSAS, metabolic disturbances |
| Hallucinations or delusions | Delirium due to infection, medications, or other causes, DLB |
| Frequent falls | PSP, DLB |
| Extrapyramidal signs or gait | Parkinsonian syndromes, VaD |
| Eye-movement abnormalities | PSP, Wernicke's encephalopathy |

*Source:* Modified from Kawas CH. N Engl J Med 2003;349: 1056–1063. For abbreviations see list on page XV

### 5.2.6 Neuroimaging Strategy and Findings in AD

All current criteria stipulate that structural imaging needs to be done at the initial evaluation of a patient suspected to have dementia. Although mainly based on the assumption that this is needed to exclude other brain diseases amenable to (surgical) treatment, this has evolved over time to include imaging to identify the earliest and most specific changes that would allow a diagnosis of AD.

#### 5.2.6.1 CT and MRI Findings

The choice between CT and MRI depends on many factors, including clinical suspicion (a priori chance), contraindications, costs and quality of scanners, claustrophobia, and the ability of the patient to keep still for the time needed for the MRI; see Table 5.5.

**Table 5.5** Neuroimaging in AD: modalities and common findings

| Option | Modality | Result |
|---|---|---|
| Rule out structural lesion | CT = MRI | Tumour, hydrocephalus, subdural hematoma |
| Hippocampal atrophy | MRI > CT | Symmetric atrophy; slight asymmetry sometimes |
| Cerebral atrophy | MRI = CT | Biparietal atrophy; precuneus atrophy |
| White matter changes | MRI > CT | None to moderate changes, symmetric, frontal > parietal |
| Microbleeds | MRI | None to many, usually lobar |
| Lacunes | MRI > CT | None to a few, most often in basal ganglia |
| Hypometabolism | FDG-PET | Temporal, parietal, post. cingular usually symmetrical |
| Hypoperfusion | SPECT = PET | Biparietal-temporal |
| Amyloid plaques | Amyloid-PET > FDDNP PET | Binding in frontal, temporal and parietal lobes |
| Dopaminergic transport and receptors | SPECT/PET | normal |

The sign = denotes modalities equally effective; > denotes one superior over the other. For abbreviations see list on page XV

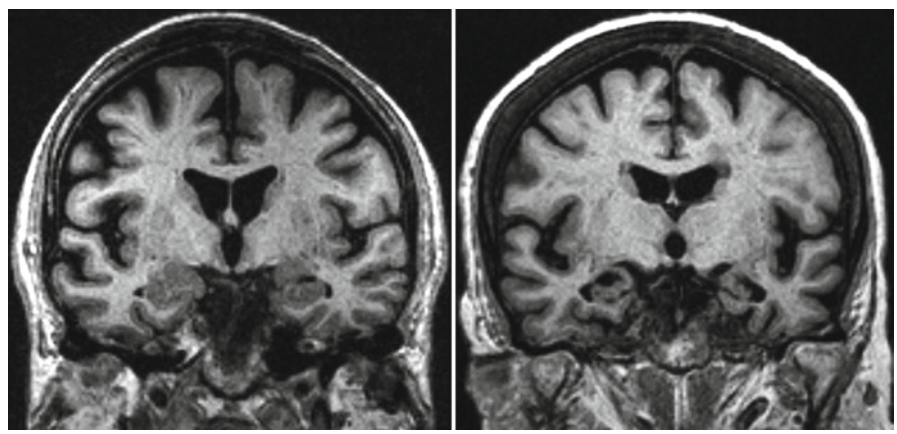


**Fig. 5.8** Hippocampal atrophy in AD. Coronal T1-weighted MRI scans of control (*left*) and patient with AD (*right*). Both subjects are 70 years old. The patient with AD shows marked atrophy of the medial temporal lobe, including disproportionate hippocampal atrophy

The microscopic histological changes in the neurodegenerative diseases are inevitably associated with progressive regional and global brain atrophy, which may be assessed in vivo using MRI. In AD, focal atrophy in the medial temporal region, including the hippocampus, has been the focus of extensive study. It reflects the typical pattern of progression of (tangle) neuropathology, spreading from the entorhinal cortex and hippocampus to the association cortices, as described by Braak and Braak. Neuropathological studies have shown that hippocampal volumes, as measured using MRI, correlate well with the neuropathological burden at post-mortem. Many studies initially using CT and later MRI and more recently again using multislice CT (see Chap. 3) have assessed the diagnostic value of hippocampal atrophy for AD. In a meta-analysis of studies using visual and linear measurements of medial temporal lobe atrophy (MTA) on MRI, the overall sensitivity and specificity for detection of AD compared with controls was estimated to be 85% and 88% respectively. In clinical practice, simple visual rating scales estimating hippocampal atrophy are useful (see Table 3.5). A striking example is shown in Fig. 5.8.

As a cautionary note, it should be emphasized that hippocampal atrophy may occur in other diseases as well; so rating MRI scans for MTA should not be done out of clinical context (see Table 5.6 for differential diagnosis)

Besides the existence of medial temporal lobe atrophy, the most important structural imaging feature of AD is *progression* of atrophy. A yearly decline in hippocampal volume approximately 2.5 times greater in patients with AD than in normal aged subjects is reported and a relationship exists between memory loss and hippocampal damage across the spectrum from normal aging to dementia.

However, neuroanatomical changes over time may be too mild, diffuse, or topographically complex to be detected by simple visual inspection or even with manually traced measurements of regions of interest.

**Table 5.6** Differential diagnosis of hippocampal atrophy

| Side | DD | Other MR findings | Clinical clues | Additional tests |
|---|---|---|---|---|
| Bilateral | AD | Temporo-parietal atrophy | Episodic memory loss | CSF, FDG, PIB |
| | Hippocampal Sclerosis | Isolated finding | Episodic memory loss | None |
| | FTLD | Temporal pole or frontal atrophy | Behavioural, language | FDG – frontal hypoperfusion |
| | DLB (late) | Diffuse cortical atrophy | Visual hallucinations, extrapyramidal | Dopamine PET/SPECT |
| Unilateral | FTLD | Anterior more than frontal, temporal pole, frontal lobe atrophy | Behavioural, language | FDG frontal hypoperfusion |
| | Mesial temporal sclerosis | High signal hippocampus | Epilepsy | EEG |

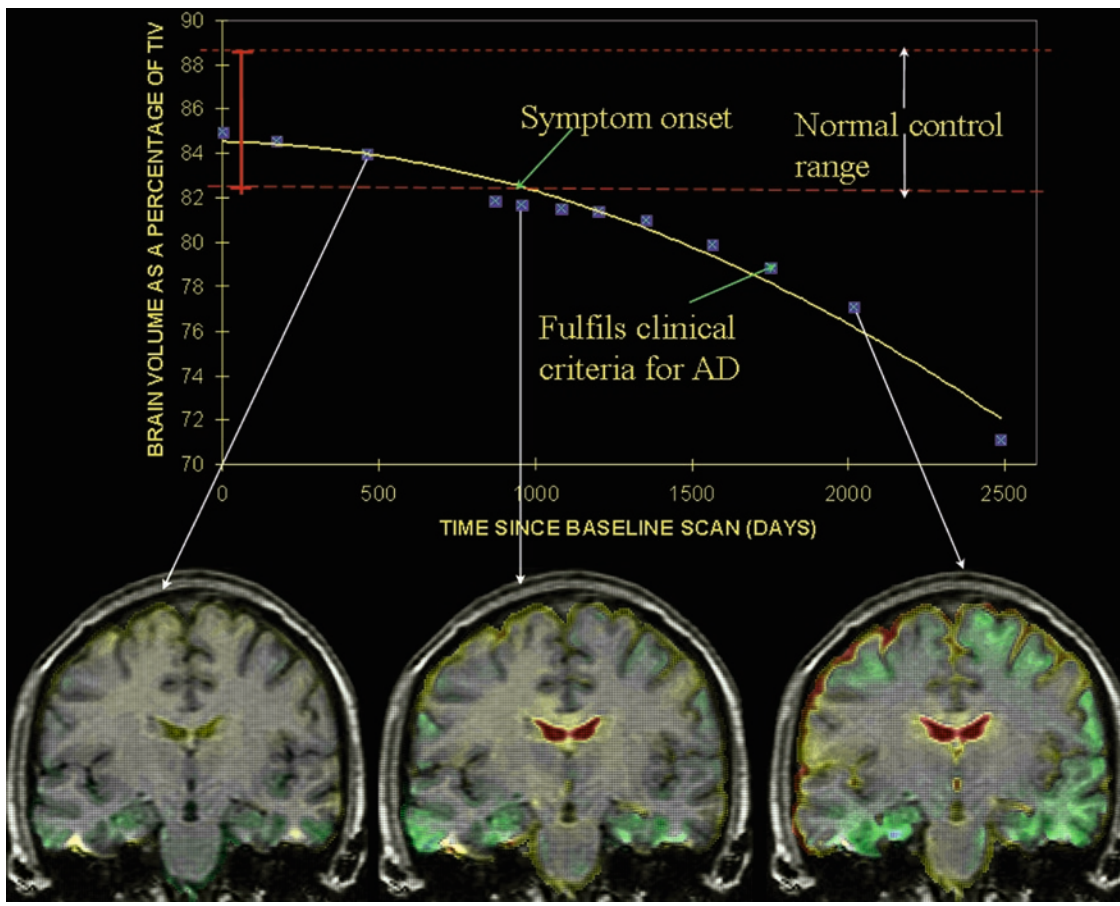



**Fig. 5.9** Serial MRI in pre-symptomatic familial AD. Graph shows brain volume changes (derived from serial T1-weighted brain MRI) over a 7 year period spanning symptom onset in an individual with familial AD (PS1 mutation). *Lower* images show scans registered to baseline with fluid *overlay* – *green*=loss of brain volume; *yellow–red*=expansion of CSF regions. Note the pre-symptomatic hippocampal atrophy and prominent loss over time

New serial volumetric imaging techniques developed in the last few years represent an added value to identify subtle structural brain changes, which have brought extensive neocortical changes to the fore. Studies of MCI subjects and asymptomatic individuals at risk for familial AD show that hippocampal, cingulate and generalised neocortical losses are all present at an early and even presymptomatic stage (see Fig. 5.9).

In clinical practice, the pattern of atrophy across the entire brain should be taken into account, rather than an isolated evaluation of the medial temporal lobe. Usually, AD is characterized by global atrophy with prominent atrophy of the medial temporal lobe. However, prominent posterior atrophy is prevalent among younger AD patients and more often in APOE4 non-carriers (Figs. 5.10 and 5.12). Atrophy of either the parietal lobe or the precuneus (including the posterior cingulate) may be the only finding in young-onset AD, and the finding of a normal hippocampus should not distract from the diagnosis of AD. The differential diagnosis of posterior/parietal atrophy is listed in Table 5.7.

Besides atrophy, cerebrovascular pathology has been associated with AD, especially in the late onset form. As such, overlap with vascular dementia (VaD) may occur and patients may actually fulfil both criteria for AD and VaD. Unfortunately, no operational criteria for so-called mixed dementia exist, so it is left to the judgement of the clinician, what label fits best with the clinical picture of the patient. Further, use of PET or CSF may help to tease out the relevant pathologies.

In AD, most often, signs of small vessel disease are present on MRI in the form of white matter hyperintensities (WMH), lacunar infarcts (lacunes) and microbleeds (Fig. 5.11.) Microbleeds have been associated with amyloid angiopathy, but their clinical relevance is still uncertain in AD (see Box 5.1 and Fig. 5.11).

As with clinical findings there are numerous 'red flags' on structural imaging that should prompt the clinician to reconsider a diagnosis of AD. In Table 5.8 the most prominent ones are summarized.

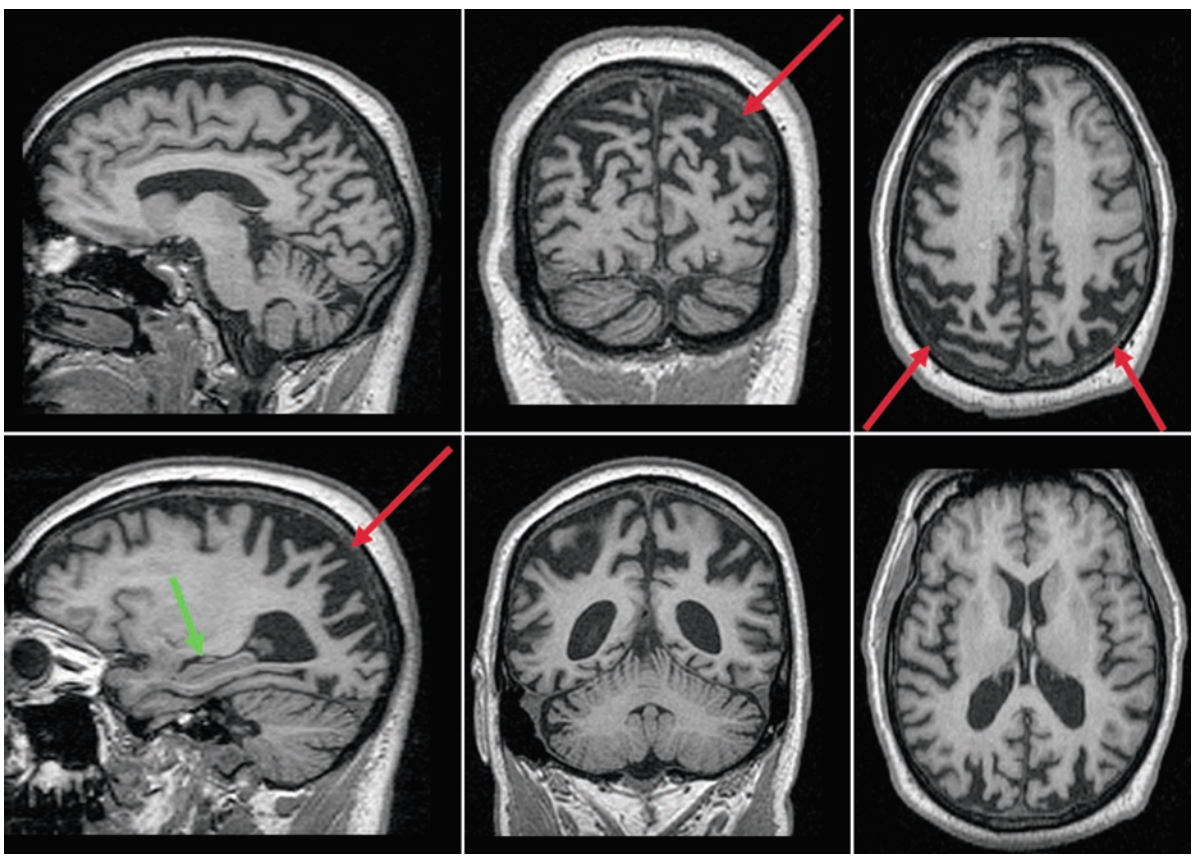


**Fig. 5.10** Posterior cortical atrophy in AD. This 58-year-old presented with cognitive decline characterised by marked visuospatial and praxis difficulties with relatively preserved memory – she had gone to the opticians several times to change her glasses (with no benefit) because she was aware of her difficulties in 'seeing' things. Note the prominent posterior cortical atrophy (*red arrows*) with preservation of the hippocampus (*green arrow*)

**Table 5.7** Differential diagnosis of posterior/parietal atrophy

| DD | Other MRI findings | Clinical clues | Additional tests |
|---|---|---|---|
| AD | Symmetrical (usually) biparietal atrophy (+/−occipital); hippocampal atrophy relatively late feature | Memory not completely normal, apraxia, visuospatial deficits | CSF, PIB |
| DLB | Generalised atrophy; parietal and occipital | Extrapyramidal signs, hallucinations, fluctuations | Dopamine imaging |
| CBD | Asymmetric parietal (and frontal) atrophy | Asymmetrical limb praxis, myoclonus | Dopamine imaging, FDG-PET |
| CJD (Heidenhain variant) | FLAIR and DWI abnormal – cortical ribbon or striatum. May have generalised cerebral and cerebellar atrophy | Rapid decline, myoclonus | EEG (may be normal), CSF (tau &14-3-3) |
| Cerebrovascular | FLAIR/T2 signal change, watershed distribution | Subcortical clinical features; stroke | Vascular risk factors |

For abbreviations, see list on page XV

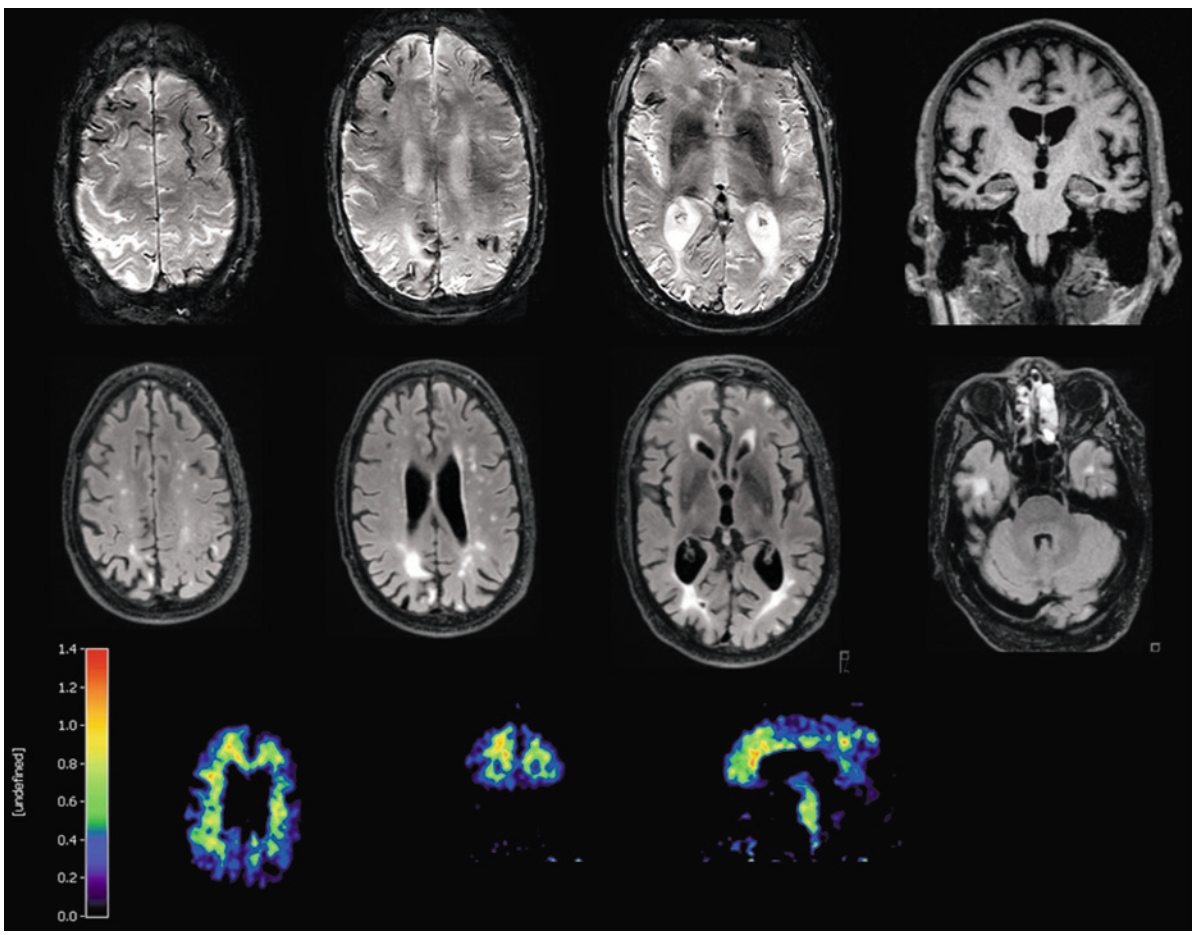



**Fig. 5.11** Amyloid angiopathy in AD. This 58-year-old man presented with memory complaints, loss of orientation, inability to use house-hold tools and perform activities of daily living. His MMSE was 24/30. MRI showed minimal hippocampal (*upper right*) and parietal atrophy, expected for age; in addition, moderate white matter changes on FLAIR (*middle row*) and multiple microbleeds and sub-pial hemosiderin (low signal in *upper row*). The clinical diagnosis was early-onset AD and PIB-PET revealed increased cortical binding (*lower row*)

**Box 5.1 Facts about microbleeds (MBs)**

- Incidental findings on MRI, occur more frequently in AD
- Prevalence related to MR field strength and MR acquisition parameters
- Lobar MBs probably related to (amyloid) angiopathy
  - Accompanying superficial siderosis suggests amyloid angiopathy
- Central MBs related to hypertensive angiopathy
- Related to worse outcome in dementia
- Caution when oral anticoagulants are needed

#### 5.2.6.2 Positron Emission Tomography (PET)

Metabolic changes may precede structural brain changes and can be visualised using the metabolic tracer [18F]fluorodeoxyglucose (FDG). In AD, temporal, parietal and most notably, posterior cingulate hypometabolism is found, discriminating AD patients from controls with good discriminatory power (sensitivity and specificity in the range of 85–90%) (Fig. 5.12). In current clinical guidelines, routine FDG-PET is not advised, since the added value over clinical diagnosis and structural imaging is uncertain. FDG-PET can be useful in the differential diagnosis between AD and FTLD.

An exciting novel application of PET is the in vivo imaging of amyloid. The amyloid β protein is considered essential in the pathogenesis of AD. Several PET tracers have been developed for this purpose. The Pittsburgh compound B ([11C]PIB) (see Sect. 3.5.3.2) is the most widely studied amyloid tracer in AD patients (Figs. 5.12 and 5.13). The future development of $^{18}$F-labelled PIB or other compounds such as AV45 or Florbetaban with a slower radioactive decay will greatly facilitate clinical implementation of amyloid imaging, which is currently restricted to centres with a cyclotron for on-site production of the tracer.

In vivo amyloid imaging may considerably add to our understanding of the underlying pathophysiological mechanisms of AD. Furthermore, imaging of amyloid may prove to be a sensitive diagnostic marker and enable prognoses in the earliest stages of formation of neuropathology (see Fig. 5.14). It should be noted, however, that amyloid deposition is not exclusively confined to AD and also occurs in dementia with Lewy bodies and congophilic amyloid angiopathy (CAA).

In familial AD, patients may be asymptomatic for a long time, while carrying a mutation in one of the known dominant genes. Amyloid imaging (with PET-PIB) may help to identify the earliest signs of plaque deposition and may thus help to identify the best time to install future treatments aiming at removing plaques. Some amyloid imaging studies in presenilin 1 mutation carriers suggest the striatum to be the earliest site of amyloid deposition – present over a decade younger than anticipated age at onset of symptoms. When symptomatic, FAD patients additionally have neocortical and thalamic PIB deposition, although this does not appear to reach the density observed in the striatum. Cerebellar PIB deposition

**Table 5.8** Red flags on MRI/CT in patients suspected of AD

| Findings | Consider alternative diagnoses |
|---|---|
| No hippocampal atrophy | Normal aging; very mild AD, young onset AD, DLB, PCA, MCI; FTD, PSP, CBD |
| Unilateral hippocampal atrophy | Semantic dementia (FTLD) |
| Anterior but not posterior hippocampal atrophy | FTLD |
| Extreme hippocampal atrophy | Argyrophilic grain disease, FTLD: semantic dementia; tau mutations (anterior > posterior) |
| Abundant small vessel disease | VaD; CAA; amyloid angiopathy |
| Unilateral cerebral atrophy | Corticobasal syndrome, FTLD |

For abbreviations, see list on page XV

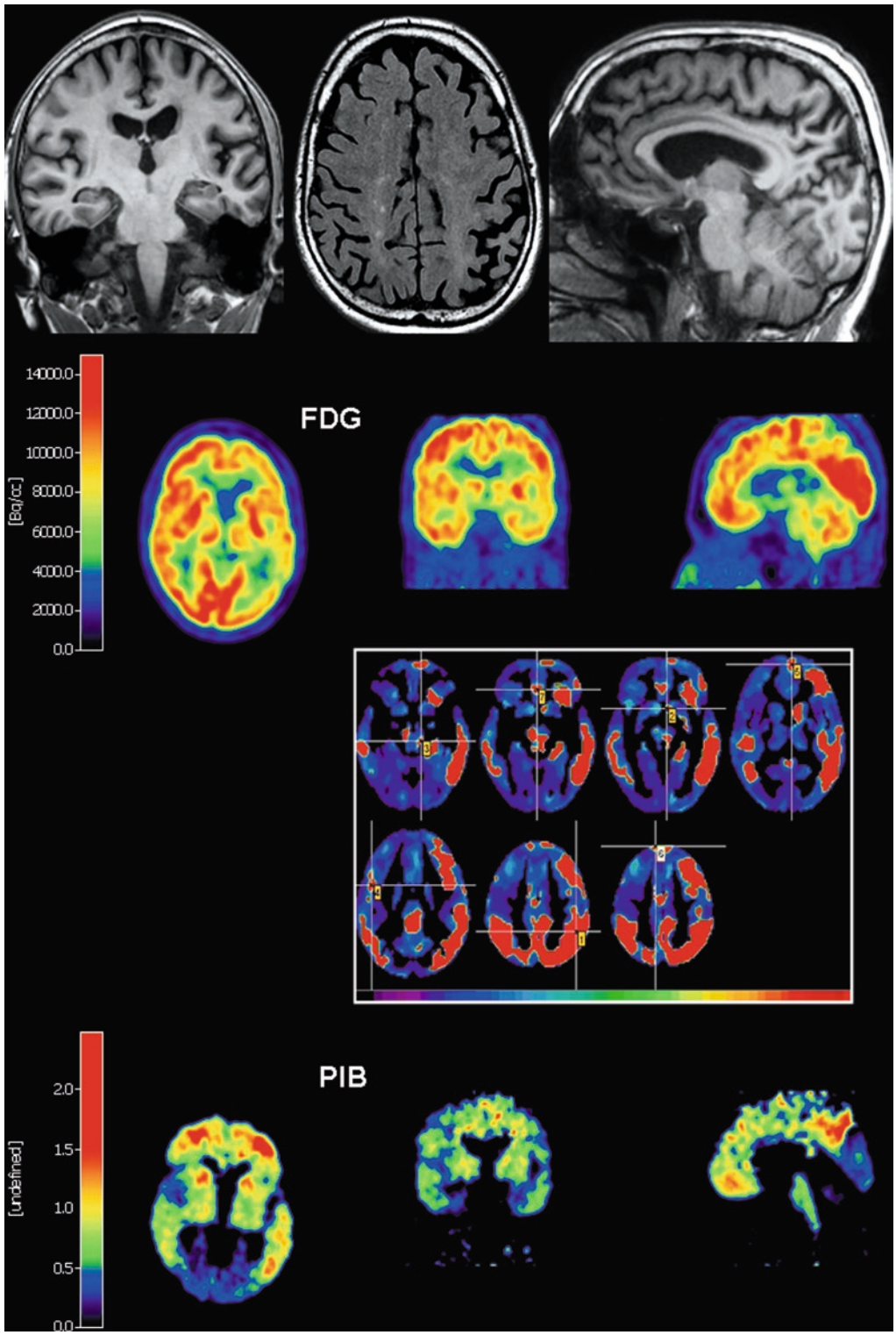



**Fig. 5.12** FDG-PET in clinically diagnosed Alzheimer's disease. This patient with presenile onset of dementia had no hippocampal atrophy, but clear parietal atrophy, asymmetric to the left hemisphere (*upper row*). FDG PET revealed reduced metabolism in the posterior cingulate and parietal association cortices, which was confirmed by voxel-wise mapping (insert) – note that also the less atrophic right parietal cortex is now clearly abnormal. The diagnosis was further corroborated by abnormal cortical PIB-binding (*lower panel*)

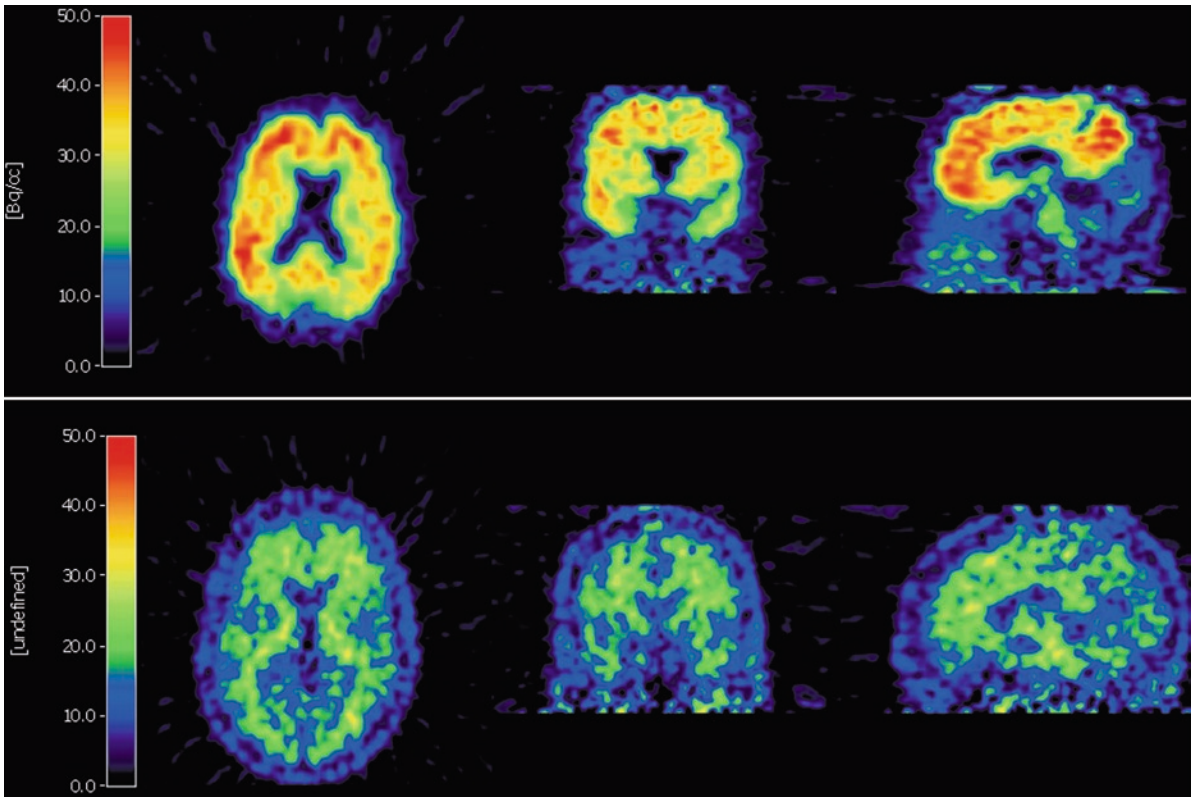



**Fig. 5.13** $^{11}$C-PIB images of a 63-year-old AD patient (*top panel*) showing abnormal cortical PIB binding in red, compared to images of a 64-year-old healthy individual (*lower panel*), showing only mild non-specific white matter binding

has also been noted in PSEN1 mutation carriers leading to the recommendation that the pons, rather than cerebellum, is used as the reference region in FAD PIB studies (Fig. 5.15).

#### 5.2.6.3 Single Photon Emission Tomography (SPECT) in AD

The most widely used tracer to study regional cerebral blood flow is $^{99}$TcHMPAO (Fig. 5.16). In AD bilateral temporo-parietal hypoperfusion is typically seen (as with FDG-PET). The application of SPECT in clinical routine has been hampered by false positive findings and insufficient added value over MRI. More promising and partly included in the routine clinical setting are *neuroreceptor* studies using $^{123}$IFP-CIT (also referred to as 'DAT-scan') which allows visualization of the degeneration of the nigrostriatal dopaminergic neurons. Scintigraphically, it allows the distinction between patients with essential tremor and patients with Parkinson's disease or PSP and MSA. In dementia, the distinction between AD and DLB may be relevant, especially when there are no extrapyramidal features. For this, the use of DAT can certainly be helpful, being abnormal in DLB, but normal in AD (see Sect. 5.4). A $^{123}$I-IBZM-SPECT shows the integrity of the post-synaptic dopamine receptor. It shows the distinction between idiopathic Parkinson's disease and diseases with parkinsonism like PSP and MSA.

### *5.2.7 Recommendations for Further Imaging*

A clinical diagnosis can be made when clinical criteria are met and MRI fits well, for instance, by showing hippocampal atrophy. The need for further work up may come up when normal findings on MRI are reported and there is clinical suspicion of AD, or in

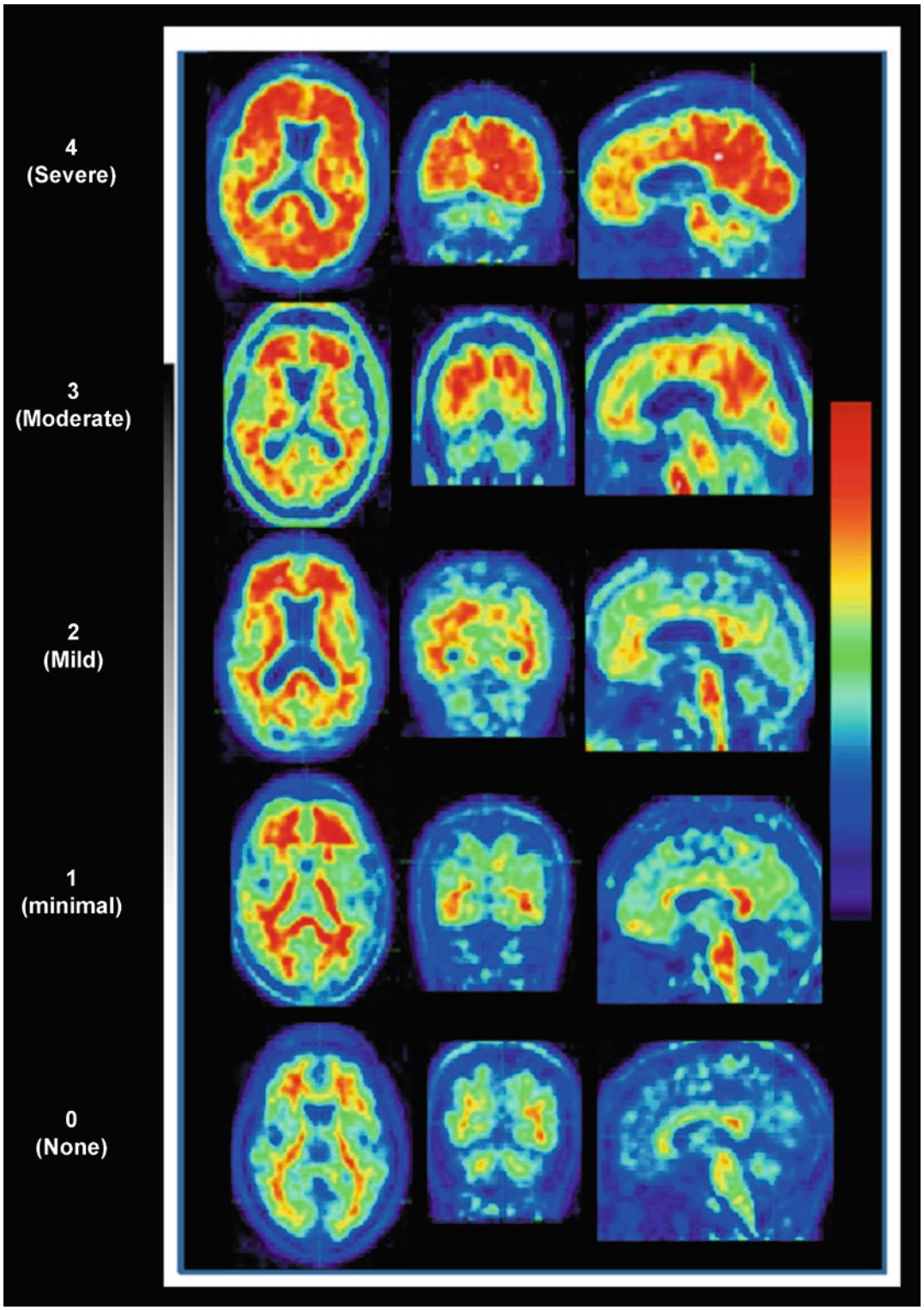



**Fig. 5.14** Amyloid imaging score. PET scans obtained with a fluorinated ligand (AV-45). This ligand allows staging of severity of binding illustrated by stages 0–4, ranging from only white matter (with no cortical) to intense neocortical binding. (Courtesy of C. Clark, M.D.)

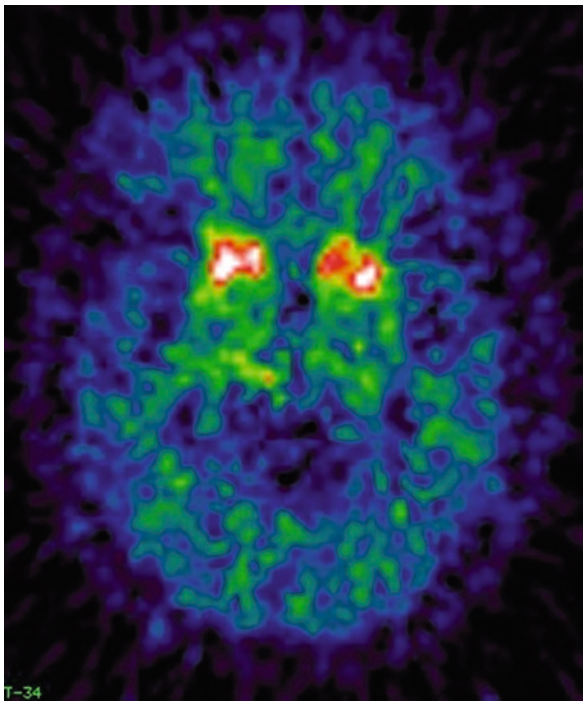


**Fig. 5.15** Prominent striatal PIB deposition (in *red*) in an asymptomatic PSEN1 mutation carrier approximately three years prior to anticipated age at onset

the case of early AD, a need arises to treat the patient in a research (randomized clinical trial) setting. MR spectroscopy in AD may show mildly reduced NAA and increased myo-inositol, consistent with axonal damage and glial proliferation. Whilst these findings are robust on a group-level, diagnostic value is not robust enough in individual cases. As outlined above, FDG-PET and especially amyloid imaging may be more sensitive in the early stage. A clear example is given in Fig. 5.12, where no hippocampal atrophy is seen in a patient suspected of early-onset AD. FDG visual and voxel-wise analyses show metabolic deficits and amyloid PET is suggestive of amyloid deposition. Also in the distinction of AD with other dementias, a dopamine SPECT scan may help to identify DLB, and an FDG PET showing most prominent frontal or temporal metabolic deficits may indicate FTD rather than AD.

#### 5.2.7.1 Repeated MRI

When to repeat a structural examination, especially MRI? There are no guidelines yet, but the 2010 EFNS guidelines mention that serial MRI may be helpful to document disease progression in a clinical setting, and may aid in the management of the patient and caregiver. An example is seen in Fig. 5.17. Changes over a

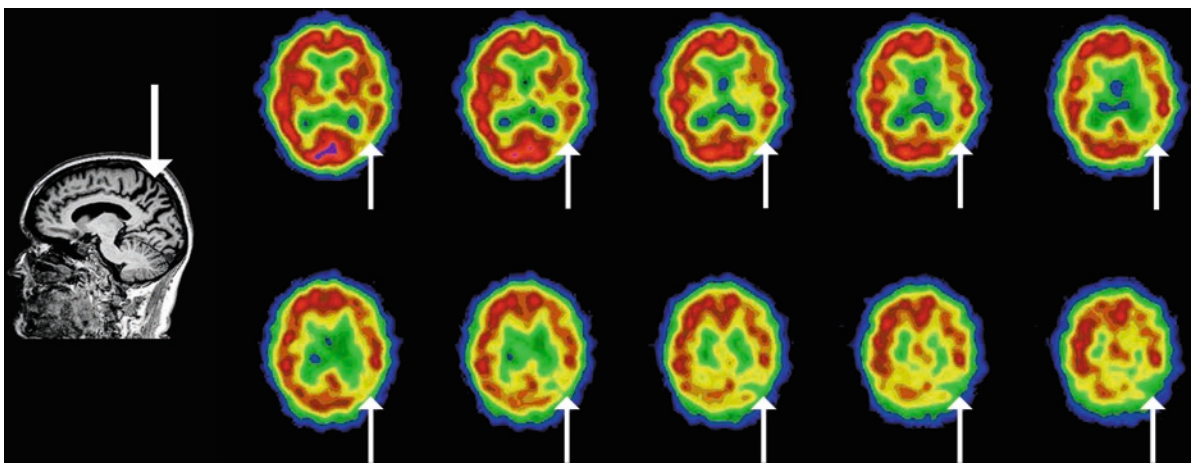


**Fig. 5.16** SPECT in AD. A 51-year-old woman that was admitted depressive symptoms, visuospatial deficits, apraxia, and minor memory loss. Parasagittal T1-weighted image (*left*) showing atrophy of the precuneus (*large arrow*) – a pattern of posterior cortical atrophy consistent with the diagnosis of early-onset AD. 99mTc-HMPAO single-photon emission computed tomography images (*right*) revealing marked brain hypoperfusion involving the left parietal lobe (*small arrows*), far beyond the regions of brain volume loss. (Reproduced with permission from *Psychiatry Res* 2010;182:287–288)

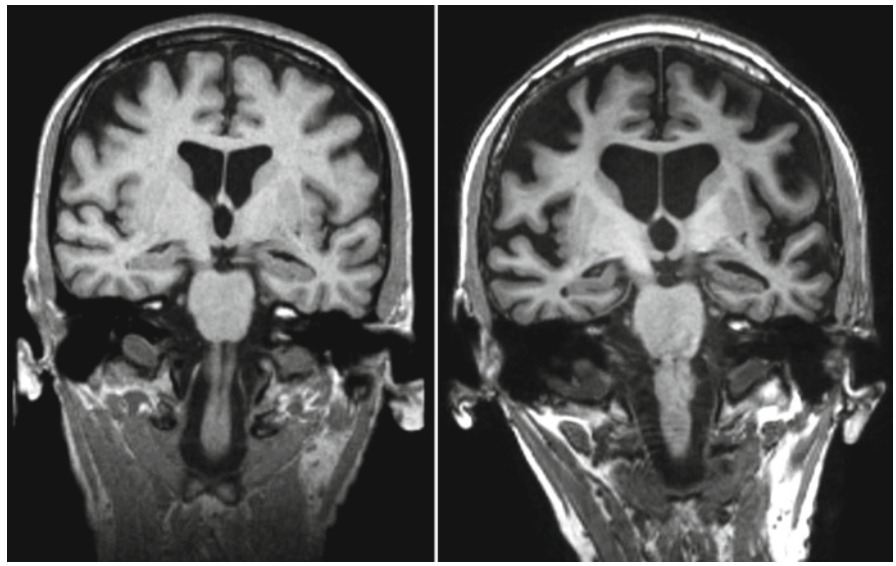


**Fig. 5.17** Serial MR images of an early-onset AD patient with rapid progression. Over 18 months time (the interval between the left and right images) this is gross loss of cortical grey matter with marked sulcal widening. Note also ventricular widening and only minimal progression of medial temporal atrophy

time period of one year that are visible to the naked eye result from volume changes that exceed those of normal ageing, and may thus strengthen the clinical diagnosis. For more subtle changes, advanced image registration techniques are needed (see Fig. 5.9).

However, in most cases, more quantitative procedures are needed to pick up changes, but these have been restricted to research use only and are being used routinely in clinical trials. Results from various groups have shown consistent loss of whole brain volume in the order of around 1.5–2% per year depending on severity, while normal ageing losses are usually below 0.5% annually.

## 5.3 Frontotemporal Lobar Degeneration

*Jonathan D. Rohrer*

### 5.3.1 Introduction and Synonyms

The terms frontotemporal lobar degeneration (FTLD) and frontotemporal dementia (FTD) describe a group of clinical syndromes which may be produced by a number of histopathologically distinct neurodegenerative causes with both sporadic and genetic aetiologies. Three *overlapping* classification systems for FTLD/FTD can be considered:

1. The clinical syndrome, for which the term FTD is often used, which reflects topography of neuronal loss/pathology and maps to a particular pattern of atrophy and hypometabolism:
   a. Behavioural variant frontotemporal dementia (bvFTD)
   b. Progressive nonfluent aphasia (PNFA)
   c. Semantic dementia (SD)
2. The histopathological syndrome, for which the term FTLD is most frequently used (tau-positive, TDP-43-positive, FUS-positive): the morphology and (especially) the immunological staining of protein inclusions.
3. The molecular genetic syndrome (*MAPT, GRN, VCP, CHMP2B, TARDP, FUS*): the gene and the type of genetic defect.

It is important, therefore, when discussing FTLD/FTD to be clear whether one is referring to a particular clinical syndrome, a specific pathology or to a genetically determined condition. The terminology can be confusing partly because pathological diagnoses, clinical syndromes and genetics are often used interchangeably and also because the nosology of FTLD has changed a number of times over recent years. Furthermore, there is an overlap between FTLD and atypical parkinsonian disorders (progressive supranuclear palsy and

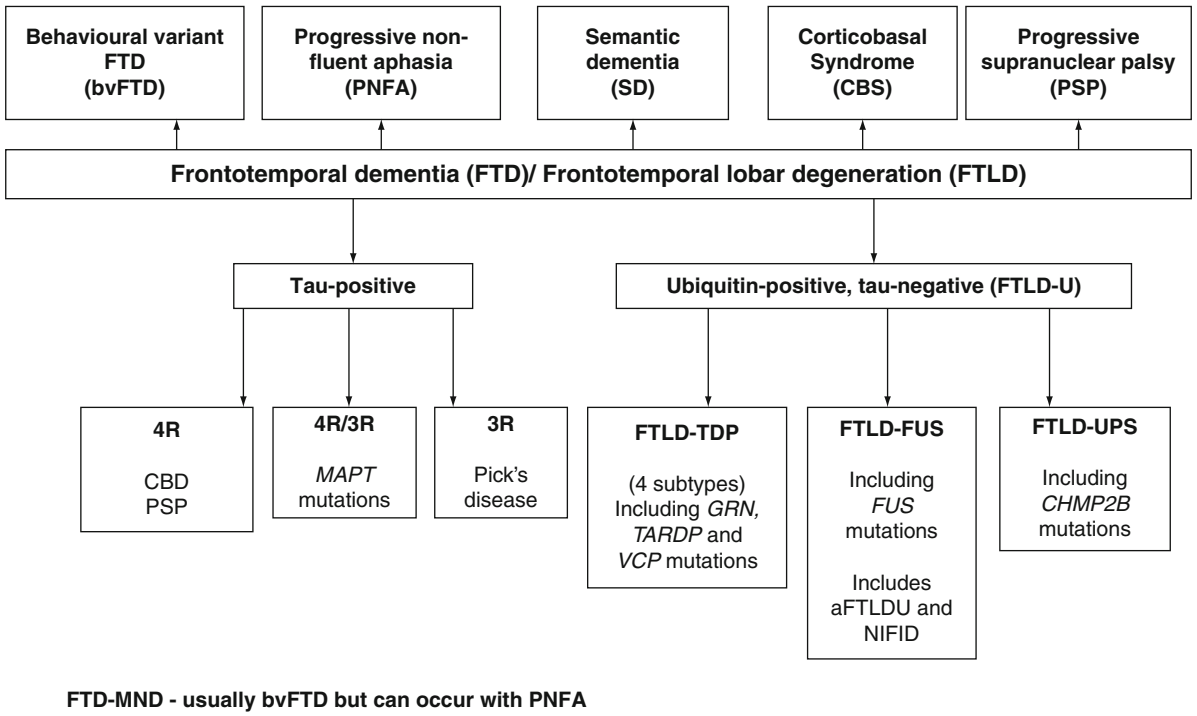



**Fig. 5.18** Summary of clinical syndromes (FTD) and genetic/pathological syndromes (FTLD). *4R* 4-repeat-tau, *3R* 3-repeat-tau, *FUS* fused in sarcoma, *UPS* unknown pathological substrate. For further abbreviations, see text

corticobasal degeneration syndromes) and also motor neuron disorders (see also chapters on parkinsonian disorders). The relationship between clinical, histopathological and genetic classifications is illustrated diagrammatically in Fig. 5.18.

**Synonyms of FTLD**

Pick's disease; Frontotemporal degeneration; Frontotemporal dementia (FTD); Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17); Frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U)

**Synonyms of the Clinical Subtypes of FTLD**

Behavioural variant frontotemporal dementia (bvFTD); Behavioural variant frontotemporal lobar degeneration (bvFTLD); Frontal variant frontotemporal lobar degeneration (fvFTLD); Progressive non-fluent aphasia (PNFA); Primary progressive aphasia (non-fluent variant); Semantic dementia (SD) Primary progressive aphasia (fluent variant); Right-temporal lobe variant of FTLD;

### 5.3.2 History and Nosology

Arnold Pick first described patients with focal atrophy of the frontal and temporal lobes in 1892 including patients both with personality change and language impairment. Although there were a few other reports of such cases in the early part of the twentieth century, in the Western world, behavioural and progressive language problems were forgotten about for many years. In Japan however, the disorder Gogi (literally 'word meaning') aphasia was described in the 1940s. The first modern accounts of the progressive language disorders in the Western literature were by Warrington (1975) and Mesulam (1982). Warrington described the selective impairment of semantic memory in a group of patients. She did not however use the term semantic dementia which was coined a number of years later. Mesulam independently described a group of patients who presented with progressive language problems including those with impairments of production and those with comprehension problems and collectively calling them primary progressive aphasia (PPA). He distinguished this from aphasia seen in other degenerative diseases such as AD by the isolated nature of the language disintegration, with many patients remaining without other cognitive or behavioural deficits for up to 10 years.

The Lund-Manchester criteria (1994, updated in 1998) later defined two variants of progressive aphasia: progressive non-fluent aphasia (PNFA) and semantic dementia (SD) as well as the behavioural variant of FTLD which they called frontotemporal dementia. Other clinical criteria for FTLD were later described by McKhann et al. 2001 with separate criteria for the progressive aphasias described by Mesulam in 2001. New criteria for both behavioural variant frontotemporal dementia and the language syndromes are in preparation. Arguments over the nosology of the progressive aphasias continues, although most authorities now agree that there are two main language syndromes that occur with FTLD pathology, namely SD and PNFA. A third variant called logopenic aphasia or the logopenic variant of primary progressive aphasia (LPA) has recently been described but appears to be more commonly associated with Alzheimer pathology rather than FTLD pathology. Overlap is seen between FTLD and two atypical parkinsonian disorders, namely corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). This led Kertesz to suggest that this group of disorders should be named the Pick Complex. There is also overlap with motor neurone disease (MND). Although only about 5–10% of patients with FTLD will have MND (termed FTD-MND) and only 5% of patients with MND will have FTLD, up to 50% of MND patients have at least mild executive dysfunction.

### 5.3.3 Epidemiology, Aetiology and Genetics

There are few epidemiological studies of FTLD and no clear environmental aetiological factors have been determined. FTLD is the third most common degenerative cause of dementia after AD and Dementia with Lewy Bodies, accounting for about 5–10% of all cases of dementia. However, FTLD commonly occurs in younger patients (45 to 65) and in this age group it is second in frequency only to AD. Despite being commoner in younger people, a wide range of ages of onset has been described from 21 years of age to mid-80s. Studies are limited, but for bvFTD prevalence probably lies somewhere between 3 and 15 per 100,000 in people over the age of 50. The prevalence of SD and PNFA is less clear, but for both syndromes it is probably similar and about half that of bvFTD. The duration of disease is also extremely variable; however, on average is around 6–10 years for FTD and PNFA but longer for SD (average 10–15 years) and much shorter for FTD-MND (average 3 years). There appears to be no difference in prevalence between men and women.

Around 30–50% of patients with FTLD have an autosomal dominant family history. Some of these families are linked to a locus on chromosome 17 and this disease group is termed FTDP-17 because an association exists between FTD and parkinsonism. Mutations in the microtubule-associated protein tau (*MAPT*) gene are causative of FTDP-17 and over 40 mutations have now been described in this gene (www.molgen.ua.ac.be/FTDmutations). Most patients present with a behavioural syndrome and/or parkinsonism (including syndromes similar to corticobasal degeneration or progressive supranuclear gaze palsy). Primary language impairment is rarely seen in *MAPT* mutations and the two prototypical syndromes of PNFA and SD are not described as occurring in this group. Mutations in another gene, progranulin (*GRN*), also on chromosome 17, have more recently been described as causing FTLD. Patients tend to present either with bvFTD or with language output impairment, commonly PNFA. Unlike *MAPT* mutations, parietal lobe deficits have also been described in *GRN* patients including presentation with a CBD syndrome. FTD associated with chromosome 3 is caused by mutations in the *CHMP2B* (charged multivesicular body protein 2B) gene and is a very rare cause of FTLD (seen mainly in a single large Danish family) presenting most commonly with bvFTD. Mutations in the *VCP* (valosin-containing protein) gene on chromosome 9 cause the syndrome of inclusion body myopathy, Paget's disease and frontotemporal dementia (IBMPFD), and similarly are a rare cause of FTLD. Rare case reports of FTLD patients with mutations in the TARDP (TAR-DNA binding protein) and FUS (fused-in-sarcoma) genes have also been described. Other loci on chromosome 9 are associated with FTD-MND but the genes are yet to be identified.

### 5.3.4 Histopathology

Macroscopically, bilateral frontal and/or temporal lobe atrophy with relative sparing of the parietal and occipital lobes is seen in FTLD (see Fig. 5.19). This may be symmetrical (particularly when just affecting frontal lobes), but is often asymmetrical and can be strikingly so; an antero-posterior gradient is typical.

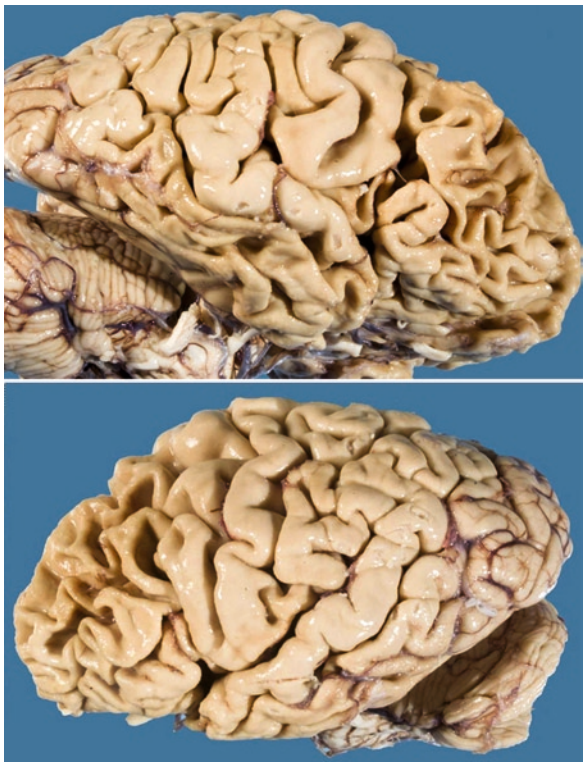


**Fig. 5.19** Macroscopy of FTLD. Note the selective severe atrophy of the frontal gyri

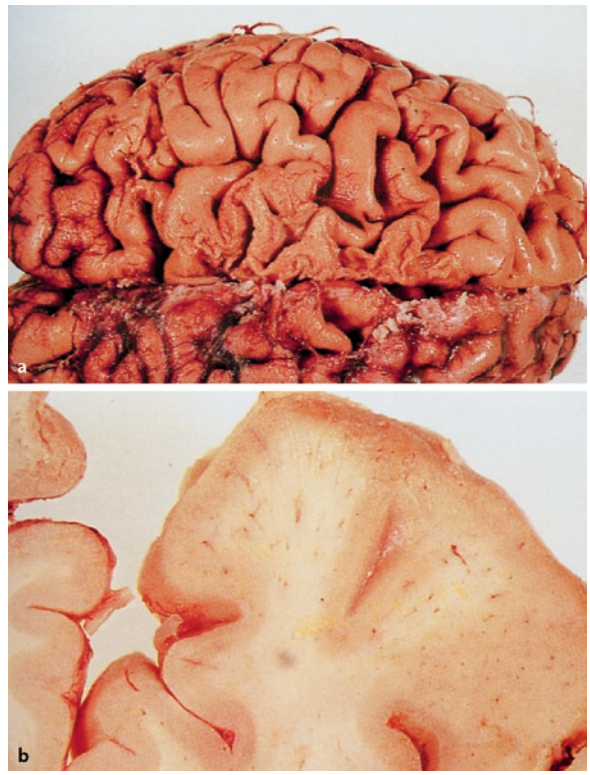



**Fig. 5.20** Pathology of CBD. Macroscopic findings in a pathological specimen of a patient with corticobasal degeneration (CBD). (**a**) At gross inspection there is circumscribed cortical atrophy in the superior frontal and anterior parietal gyrus. (**b**) The coronal section shows thinning of the cortical grey matter and underlying white matter. (Courtesy of T. Revesz, M.D., and S.E. Daniel, M.D.)

Neuropathological criteria have been described by Cairns et al. (2007) and updated recently by Mackenzie et al. (2010). There are three main subdivisions of histological findings: tau-positive inclusions, TDP-43-positive inclusions and FUS-positive inclusions (Fig. 5.18). Only a small minority of patients with FTLD do not have one of these three pathologies including patients with CHMP2B mutations and those lacking any inclusions. The tau-positive group can be subdivided into three groups on the basis of the relative proportions of four or three repeat tau (Fig. 5.18). The tau-positive includes classical Pick's disease, a diagnosis which historically required the presence of Pick bodies which are ubiquitin and tau-positive inclusions – Pick bodies turn out to have predominantly three-repeat tau. Also, within the tau-positive group are the *MAPT* mutations as well as CBD (Fig. 5.20), PSP and the relatively rare argyrophilic grain disease. The TDP-43-positive group includes four subtypes; patients with *GRN*, *VCP* and TARDP mutations have TDP-43-positive pathology. The recently described FUS-positive pathological group includes cases previously described as atypical FTLD with ubiquitin-positive inclusions and cases with neuronal intermediate filament inclusion disease (NIFID). Clinico-pathological correlation remains complex, but certain patterns are starting to emerge through large studies of clinically well-defined patients; e.g. TDP-43-positive pathology is associated with the clinical syndromes of SD and FTD-MND, while most clinical PSP cases are associated with tau pathology.

It is also important to recognize that rarely each of the FTD clinical syndromes can be associated with AD pathology i.e. a prominent and primary behavioural or language syndrome indistinguishable from bvFTD, PNFA or SD may occur. Also, the term 'frontal AD' is used by some people to indicate a clinical syndrome in which patients have features of episodic memory impairment characteristic of AD and also early behavioural symptoms characteristic of bvFTD. Some patients that present with the clinical picture of bvFTLD may turn out to have AD (Fig. 5.21).

### 5.3.5 Clinical Features and Imaging Strategy

While CT can be helpful to exclude other pathology involving the fronto-temporal region (e.g. a meningioma), MRI is the method of choice to demonstrate (early) atrophy (e.g. in the orbitofrontal region and/or temporal pole). Coronal images are particularly relevant as they allow assessment of asymmetry in the (medial) temporal lobe structures (Fig. 5.22).

#### 5.3.5.1 Behavioural Variant Frontotemporal Dementia (bvFTD)

BvFTD presents with insidious change in personality and behavioural symptoms (Box 5.2). Common presenting symptoms include apathy or social withdrawal, disinhibition or inappropriate social behaviour and loss of empathy. Loss of insight is characteristic and other behavioural symptoms are seen: perseverative or stereotyped behaviour, mental inflexibility, obsessiveness, hoarding, poor self-care, distractibility and a change in eating behaviour, in particular development of a sweet tooth. Patients may often initially be thought to have non-organic psychiatric disorders. Executive dysfunction with poor planning and problem-solving is also seen although this can dissociate from behavioural changes.

Language symptoms include a decrease in the amount of speech (although commonly without errors), perseverative use of certain phrases and echolalia; many patients will become mute as the disease progresses. MMSE scores can be entirely normal early in the disease because it does not test executive function and also because behavioural features may predominate without significant cognitive impairment. Although there are no curative treatments, management of the behavioural features is important.

Atrophy of the frontal and temporal lobes is best seen on (coronal) T1-weighted images (Fig. 5.23 and 5.24). Characteristically in bvFTD, there is fronto-temporal atrophy with an antero-posterior gradient i.e. relative sparing of the parietal and occipital lobes, and this atrophy, although commonly bilateral, is often asymmetrical. T2-weighted and FLAIR imaging is useful to exclude concurrent vascular disease as well as assessing for subcortical white matter changes which have occasionally been described in pathologically confirmed cases of FTD. Although most areas of the

**Box 5.2 Criteria for behavioural variant frontotemporal dementia (from Neary et al. 1998)**

Character change and disordered social conduct are the dominant features initially and throughout the disease course. Instrumental functions of perception, spatial skills, praxis, and memory are intact or relatively well preserved.

I. Core diagnostic features

Insidious onset and gradual progression
Early decline in social interpersonal conduct
Early impairment in regulation of personal conduct
Early emotional blunting
Early loss of insight

II. Supportive diagnostic features

*Behavioural disorder*

1. Decline in personal hygiene and grooming
2. Mental rigidity and inflexibility
3. Distractibility and impersistence
4. Hyperorality and dietary changes
5. Perseverative and stereotyped behaviour
6. Utilization behaviour

*Speech and language*

1. Altered speech output
   (a) Aspontaneity and economy of speech
   (b) Press of speech
2. Stereotype of speech
3. Echolalia
4. Perseveration
5. Mutism

*Physical signs*

1. Primitive reflexes
2. Incontinence
3. Akinesia, rigidity, and tremor
4. Low and labile blood pressure

*Investigations*

1. Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder
2. Electroencephalography: normal on conventional EEG despite clinically evident dementia
3. Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality

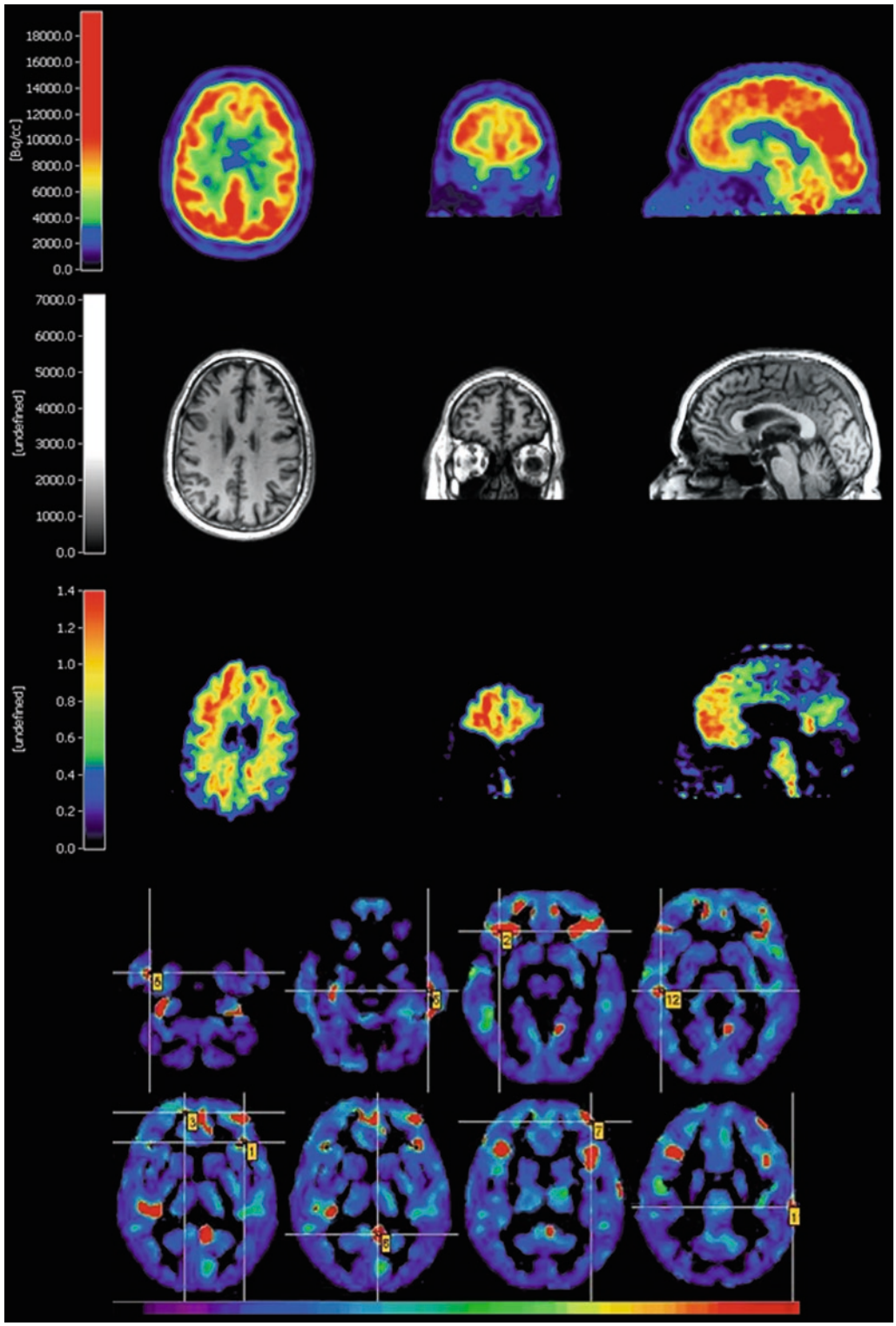



**Fig. 5.21** Behavioural variant FTD syndrome caused by Alzheimer pathology. This 63-year-old man presented with slowly progressive change in character, apathy and memory disturbances. Cognitive testing revealed mainly executive dysfunction, and less prominent memory disturbances. His mother developed AD at the age of 63. FDG-PET showed reduced frontal metabolism (*upper row*), which was confirmed using voxel-wise analysis (*bottom panel*), suggesting FTLD rather than AD. MRI showed frontal but not hippocampal atrophy (*second row*). Amyloid PET (*third row*), however, showed abnormal cortical PIB binding, consistent with AD, despite normal CSF amyloid-beta levels (slightly increased p-tau)

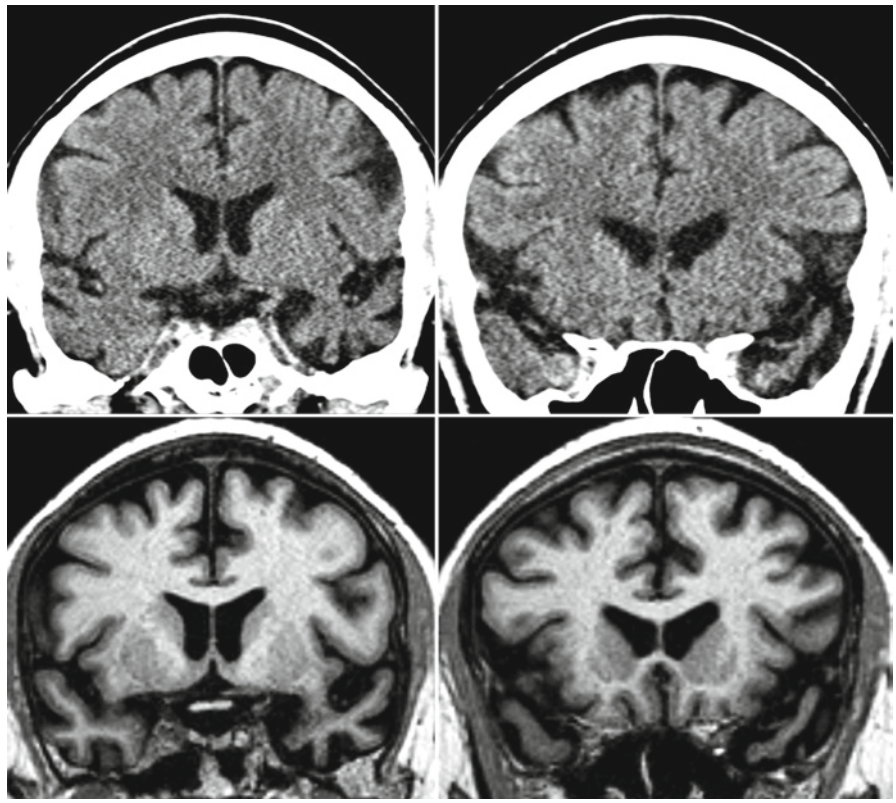


**Fig. 5.22** Comparison of coronal CT and MR in SD. Note that the coronal reformats of the multi-detector CT (*top*) are quite comparable to the coronal MR (*bottom*) images in showing left more than right anterior temporal atrophy in the same patient. (Images courtesy of Mike Wattjes)

frontal and temporal lobes can be affected during the disease, the earliest area of sulcal widening is probably the orbitofrontal cortex, followed by the mesiofrontal (interhemispheric) cortex. In more advanced cases, the dorso-lateral prefrontal cortex will also become involved. Bilateral hippocampal and amygdalar atrophy are also features of FTD, again often asymmetrical. The key point to note here though is that the medial temporal lobe is more affected anteriorly (e.g. the amygdala being more affected than the hippocampus and posterior hippocampus often appearing normal).

It should be noted that in early disease structural imaging is often normal. Although many patients will progress to show frontotemporal atrophy later in the disease, a small number of cases appear to clinically progress slowly in terms of behavioural symptoms with little or no atrophy on longitudinal MR scanning. There are few studies looking at this 'benign' variant of bvFTD, and its status within the FTLD spectrum remains unclear: some of these cases are likely to be non-neurodegenerative phenocopies and serial imaging may be helpful in distinguishing these.

The features of diffusion-weighted imaging in FTD are unclear. While no signal increase on DWI is expected in the cortex, increased mean diffusivity (MD) in various white matter regions including bilateral superior frontal gyri, right orbitofrontal gyrus, bilateral anterior temporal lobes and left middle temporal lobe have been found using DTI in the adjacent white matter.

#### 5.3.5.2 Progressive Non-Fluent Aphasia (PNFA)

PNFA presents with impairment of speech production, commonly hesitant, effortful speech or stuttering (apraxia of speech) and/or agrammatism (breakdown of syntax). Other characteristic features are phonemic paraphasias (sound-based errors), anomia and impaired repetition of polysyllabic words. There is preserved single-word comprehension early on although impaired sentence-level comprehension. Reading is also non-fluent and effortful. Writing is preserved early in the disease but becomes more affected later on with spelling and grammatical errors. Language disintegration progresses inexorably to mutism. Behavioural symptoms are rare early in the disease and there may

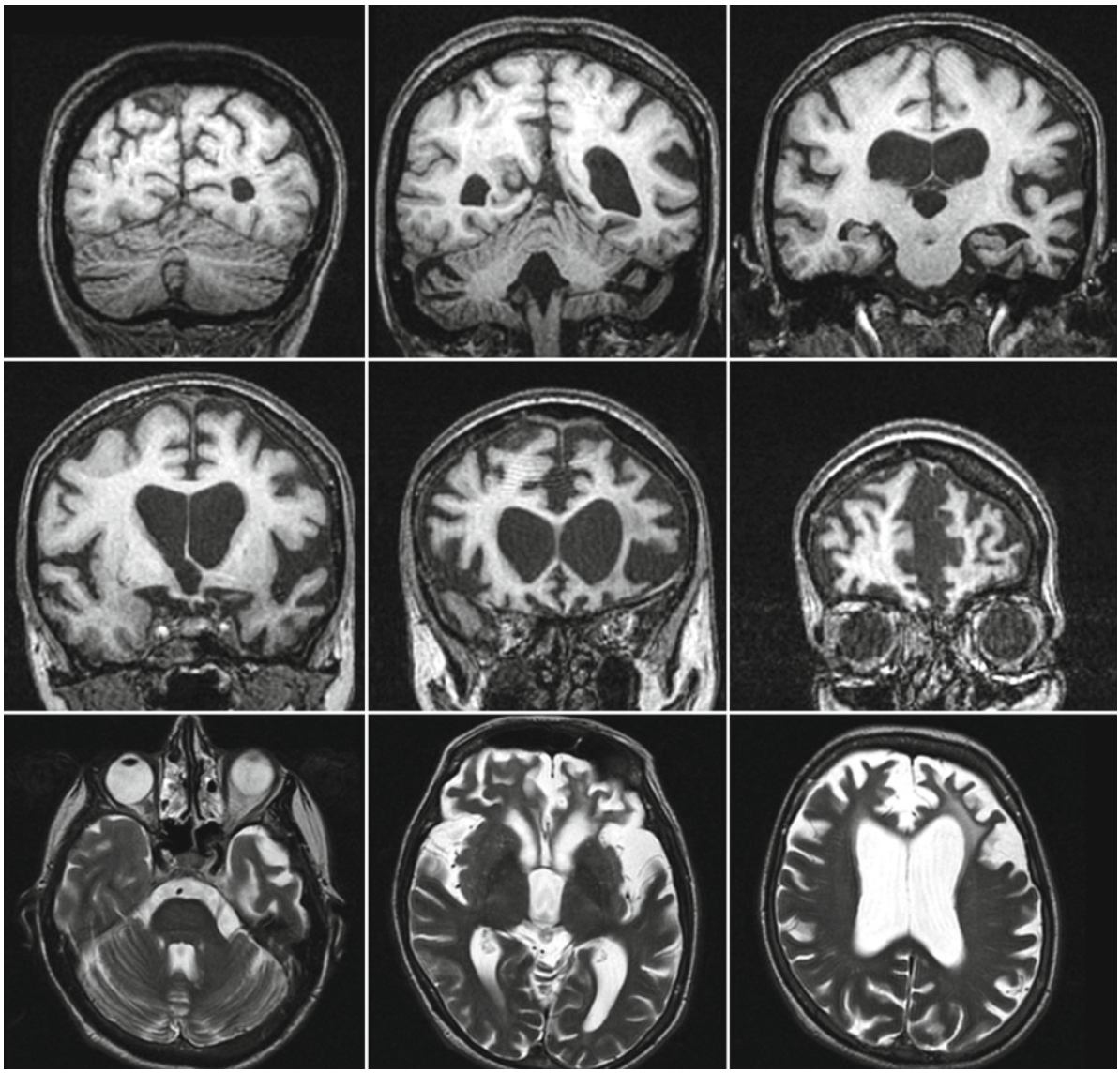


**Fig. 5.23** Behavioural variant frontotemporal dementia. Severe asymmetric frontal atrophy in a patient with confirmed TDP-43-positive inclusions at post-mortem; also note less severe involvement of the temporal lobes, with the lateral gyri more affected than the medial part

be no other features (either cognitive or behavioural) beyond the speech production disorder many years into the disease. Late behavioural changes include mental rigidity and apathy in particular. The diagnostic criteria are summarized in Box 5.3.

PNFA is heterogeneous and some patients initially present with one of agrammatism, apraxia of speech or anomia in the absence of other features. There is some evidence that the initial or predominant language phenotype predicts the underlying pathology e.g. apraxia of speech appears to be commonly associated with tau-positive pathology. A number of rare variants of progressive speech production impairment are described although their nosological status is unclear: progressive aphemia (severe speech apraxia), cortical anarthria and progressive dynamic aphasia (impaired spontaneous

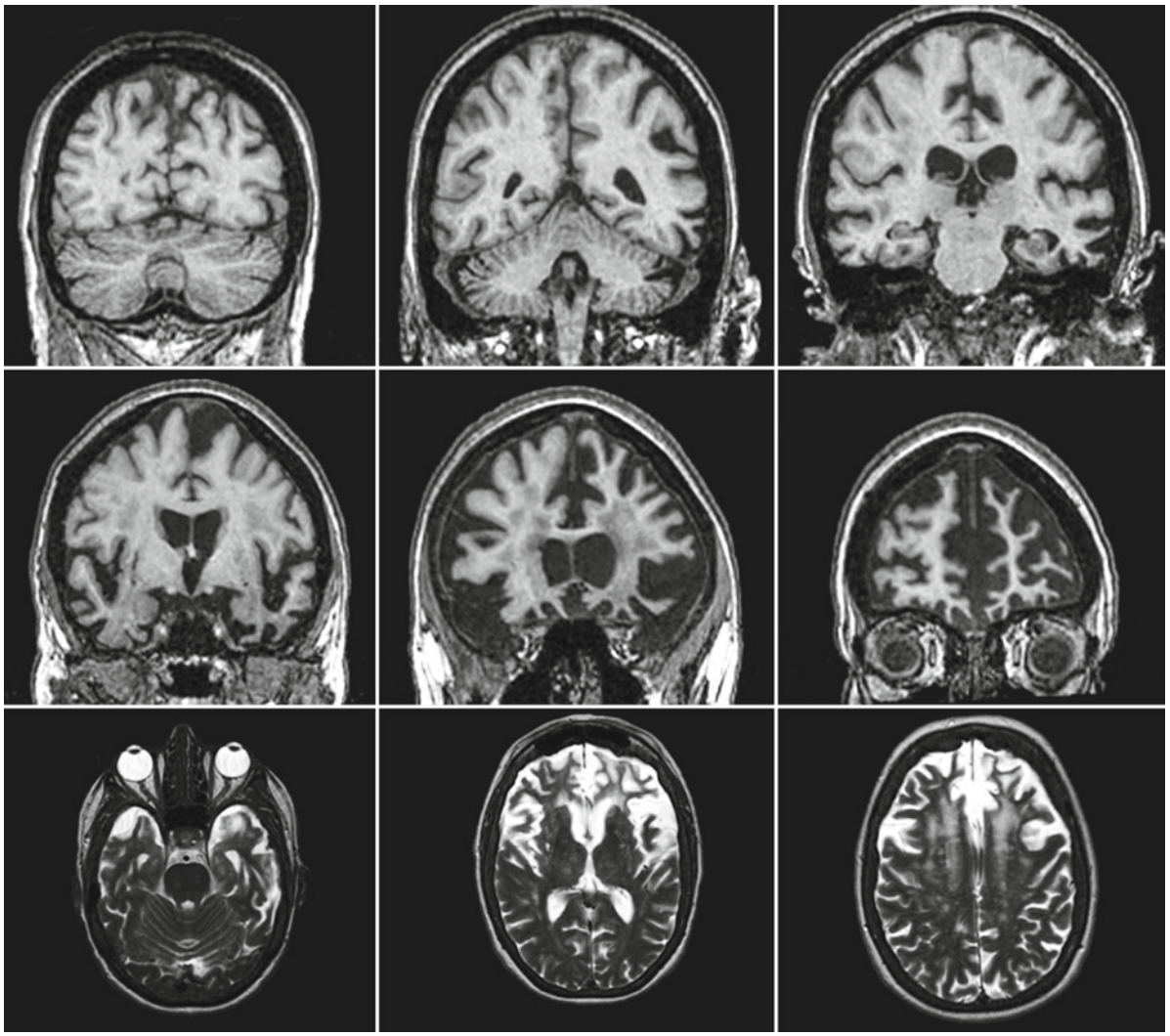


**Fig. 5.24** Behavioural variant frontotemporal dementia. End-stage bilateral severe frontal atrophy was seen in this patient with confirmed tau-positive Pick's disease at post-mortem. Note the anterior–posterior gradient of atrophy and the signal change in the very atrophic areas. Note relative sparing of the temporal lobe (especially posteriorly), and importantly relative preservation of the hippocampus

propositional speech). Such disorders may represent different stages of a common disease continuum reflecting a specific pattern of anatomical involvement or alternatively, may constitute distinct disease entities with different pathophysiological and histopathological correlates.

Imaging findings in PNFA are heterogeneous implicating a number of regions in the dominant (left) hemisphere although classically it is the left perisylvian regions, particularly the left inferior frontal and insular cortices, which are affected (Fig. 5.25) – in addition there may be involvement of left superior frontal, superior temporal and inferior parietal lobes. Variation between patients likely reflects heterogeneity of the neurolinguistic deficits in PNFA – although relation with different pathological findings in PNFA has not yet been studied in detail.

### Box 5.3 Criteria for progressive non-fluent aphasia (from Neary et al. 1998)

Disorder of expressive language is the dominant feature initially and throughout the disease course. Other aspects of cognition are intact or relatively well preserved.

I. Core diagnostic features
   Insidious onset and gradual progression
   Non-fluent spontaneous speech with at least one of the following: agrammatism, phonemic paraphasias, anomia
II. Supportive diagnostic features

*Speech and language*

1. Stuttering or oral apraxia
2. Impaired repetition
3. Alexia, agraphia
4. Early preservation of word meaning
5. Late mutism

*Behaviour*

1. Early preservation of social skills
2. Late behavioural changes similar to FTD

Physical signs: late contralateral primitive reflexes, akinesia, rigidity, and tremor

*Investigations*

1. Neuropsychology: non-fluent aphasia in the absence of severe amnesia or perceptuospatial disorder
2. Electroencephalography: normal or minor asymmetric slowing
3. Brain imaging (structural and/or functional): asymmetric abnormality predominantly affecting dominant (usually left) hemisphere

#### 5.3.5.3 Semantic Dementia (SD)

SD is characterized by loss of semantic or conceptual knowledge (see Box 5.4). It commonly presents as a fluent aphasia with empty, circumlocutory speech, loss of word meaning, anomia and impaired single-word comprehension. Patients often complain of 'word-finding difficulty' as an initial symptom. Semantic paraphasias are seen both in spontaneous speech and tasks of confrontational naming. Although language progressively decreases in amount, patients often maintain a small repertoire of stereotyped phrases. Non-verbal semantic loss also occurs and a visual

### Box 5.4 Criteria for semantic dementia (from Neary et al. 1998 modified by Adlam et al. 2006)

Semantic disorder (impaired understanding of word meaning and/or object identity) is the dominant feature initially and throughout the disease course. Other aspects of cognition, including autobiographic memory, are intact or relatively well preserved.

I. Core diagnostic features
   Insidious onset and gradual progression

   Language disorder characterized by

   1. Progressive, fluent, empty spontaneous speech
   2. Loss of word meaning, manifest by impaired naming and comprehension
   3. Semantic paraphasias and/or

   Impairment on tests of non-verbal associative knowledge
   Preserved single-word repetition
   Preserved ability to read aloud and write to dictation orthographically regular words
II. Supportive diagnostic features

*Speech and language*

1. Press of speech
2. Idiosyncratic word usage
3. Absence of phonemic paraphasias
4. Surface dyslexia and dysgraphia
5. Preserved calculation

*Behaviour*

1. Loss of sympathy and empathy
2. Narrowed preoccupations
3. Parsimony

*Physical signs*

1. Absent or late primitive reflexes
2. Akinesia, rigidity, and tremor

*Investigations*

Neuropsychology

1. Profound semantic loss, manifest in failure of word comprehension and naming and/or face and object recognition
2. Preserved phonology and syntax, and elementary perceptual processing, spatial skills, and day-to-day memorizing

Electroencephalography: normal
Brain imaging (structural and/or functional): predominant anterior temporal abnormality

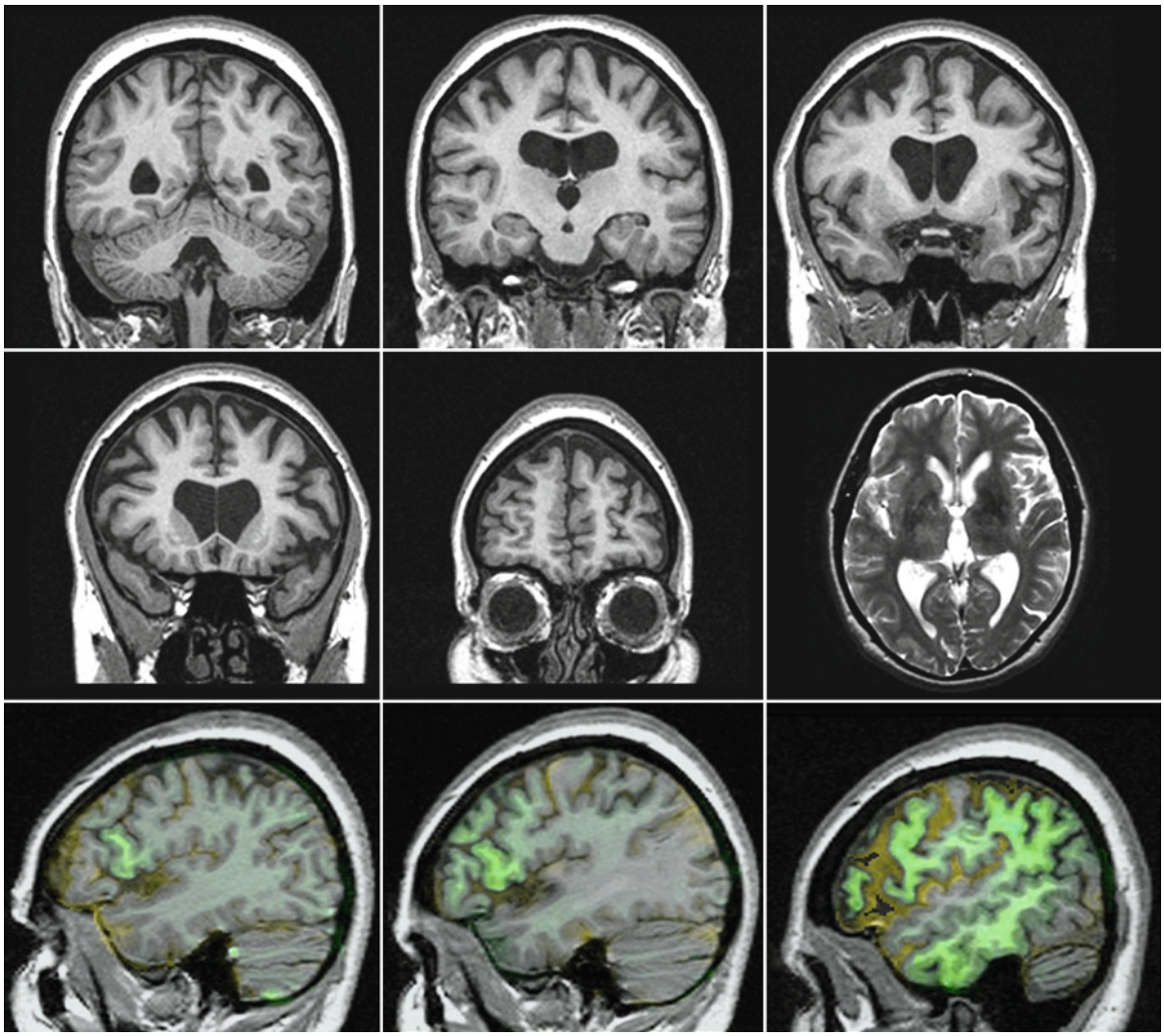


**Fig. 5.25** Progressive non-fluent aphasia. This 55-year-old woman with PNFA had serial MR imaging as part of a longitudinal study of individuals at risk of FTLD. At the time of the imaging shown in the *top two rows* (51 months from her first, and asymptomatic, scan), she had become symptomatic with difficulties with expressive language. She had speech production difficulties and made phonemic errors in spontaneous speech and in reading. She also had the beginning of orofacial apraxia at this time. The coronal T1-weighted images show frontal atrophy with asymmetrical (left>right) perisylvian fissure atrophy and more posteriorly also seen on the single T2-weighted axial image. *Bottom row* of sagittal images show deformation maps from serial MRI – green represents regions of contraction. *Left* image (0–14 months, presymptomatic) with focal antero-lateral left frontal lobe loss, particularly centred around the pars opercularis (Broca's area) presaging speech production problem; *middle* image (14–26 months), region of increased atrophy rate now spreading; *right* image (45–56 months), much more generalised atrophy. (Adapted with permission from J Neurol Neurosurg Psychiatry 2005;76:162–168)

agnosia may occur with the inability to recognize the nature of an object in the presence of normal perception. Behavioural features include disinhibition and abnormal eating behaviour in particular.

Structural imaging in SD generally reveals left greater than right temporal lobe atrophy. In particular, the temporal lobe atrophy is mainly anterior, with an antero-posterior gradient and knife-edge or 'razorback' atrophy of the anterior temporal lobe can be seen (Fig. 5.26). Temporal lobe atrophy is also mainly inferior (often severe involvement of the fusiform gyrus) with relative sparing of the superior temporal gyrus. As the disease progresses the right temporal lobe becomes more involved. Amygdalar and hippocampal atrophy occurs but is asymmetrical with normally left greater than right atrophy and again

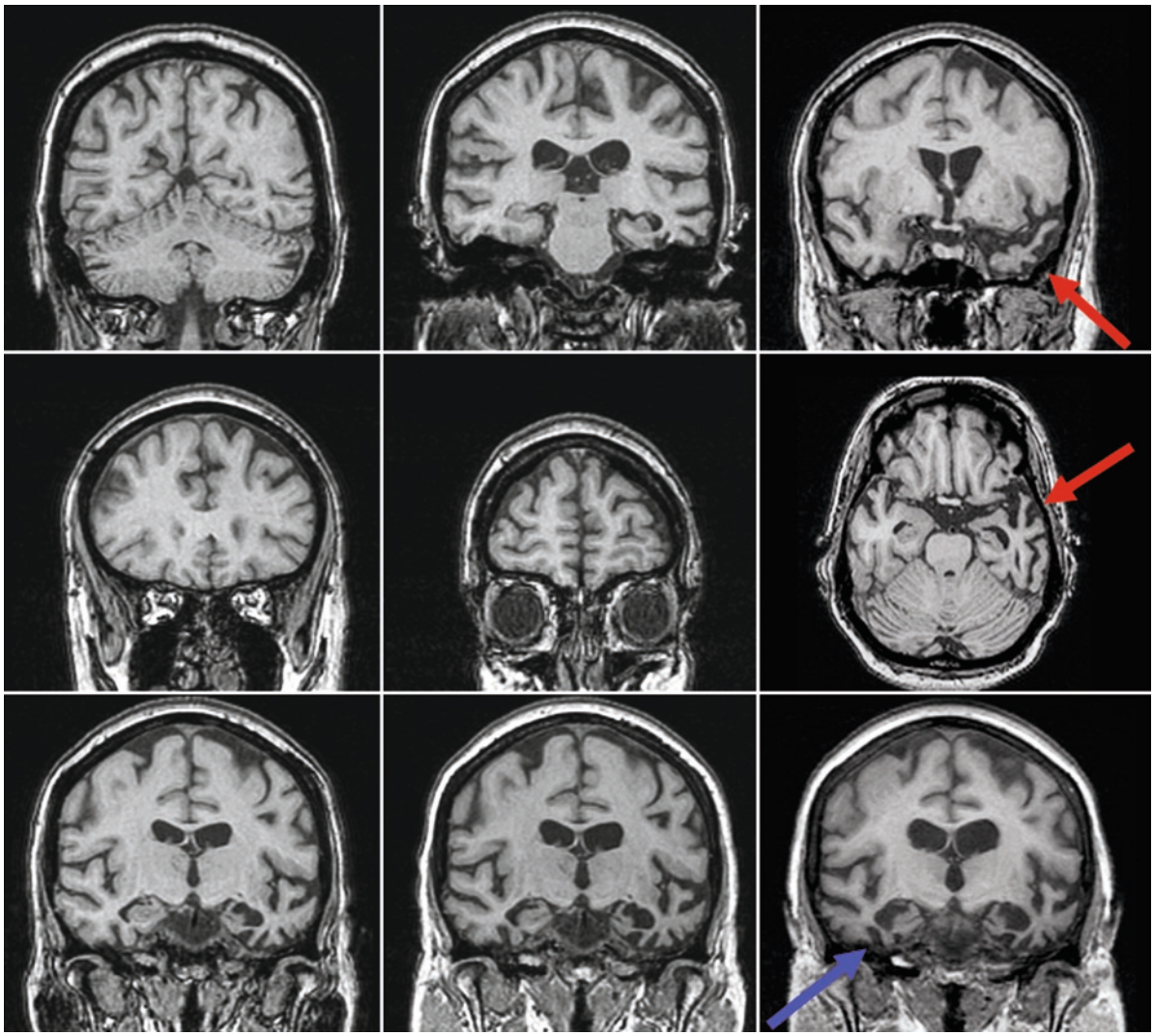


**Fig. 5.26** Semantic dementia. Patient with confirmed TDP-43-positive inclusions (type 1) at post-mortem. *Top rows* show isolated left-sided atrophy of the temporal pole (*red arrows*) at presentation. Registered serial images (*bottom*) from baseline to 2 years (*middle*) and 4 years (*right*) show spread to the right side (*blue arrow*); note the fusiform and inferior anterior temporal lobe atrophy

a marked anterior greater than posterior atrophy gradient – so the amygdala is more affected than the hippocampal head which is in turn more affected than the body of the hippocampus. These features are very useful in distinguishing SD from AD. The clinical syndrome of SD can sometimes occur in patients with right greater than left temporal lobe atrophy.

#### 5.3.5.4 Logopenic Aphasia (LPA)

Patients with LPA are most commonly found to have Alzheimer pathology at post-mortem. They present with long word-finding pauses in their speech and may have anomia and impaired phonological working memory. Parietal lobe features (e.g. limb apraxia and

dyscalculia) are also seen. Imaging shows an asymmetrical pattern of atrophy with predominant left posterior temporal cortex and inferior parietal lobule involvement with progression to involve the posterior cingulate and more anterior temporal lobe areas including the hippocampus.

#### 5.3.5.5 Corticobasal Degeneration (CBD)

CBD is covered in more detail under Sect. 5.4 and the inclusion of CBD in more than one place in this book is symbolic of the position that CBD occupies, with overlap (and clinical uncertainty) involving FTLD and AD as well as Parkinson's disease and other extrapyramidal disorders. Although cognitive and behavioural symptoms were originally thought to be rare in patients with a CBD syndrome (also called corticobasal syndrome or CBS to distinguish the clinical syndrome from the pathological syndrome of CBD), it is now clear that they form a major part of the syndrome and the overlap with both bvFTD and PNFA is well-described.

Imaging often reveals asymmetrical fronto-parietal atrophy with relative sparing of the temporal and occipital lobes with either hemisphere being predominantly affected. However, imaging findings are heterogeneous which is likely to represent at least in part the variable pathological causes of a CBS: although most commonly a tauopathy (CBD or rarely PSP pathology), CBS can also be caused by Alzheimer pathology and FTLD-TDP pathology. Detailed imaging studies of pathologically confirmed tau-positive CBD are limited (Fig. 5.27).

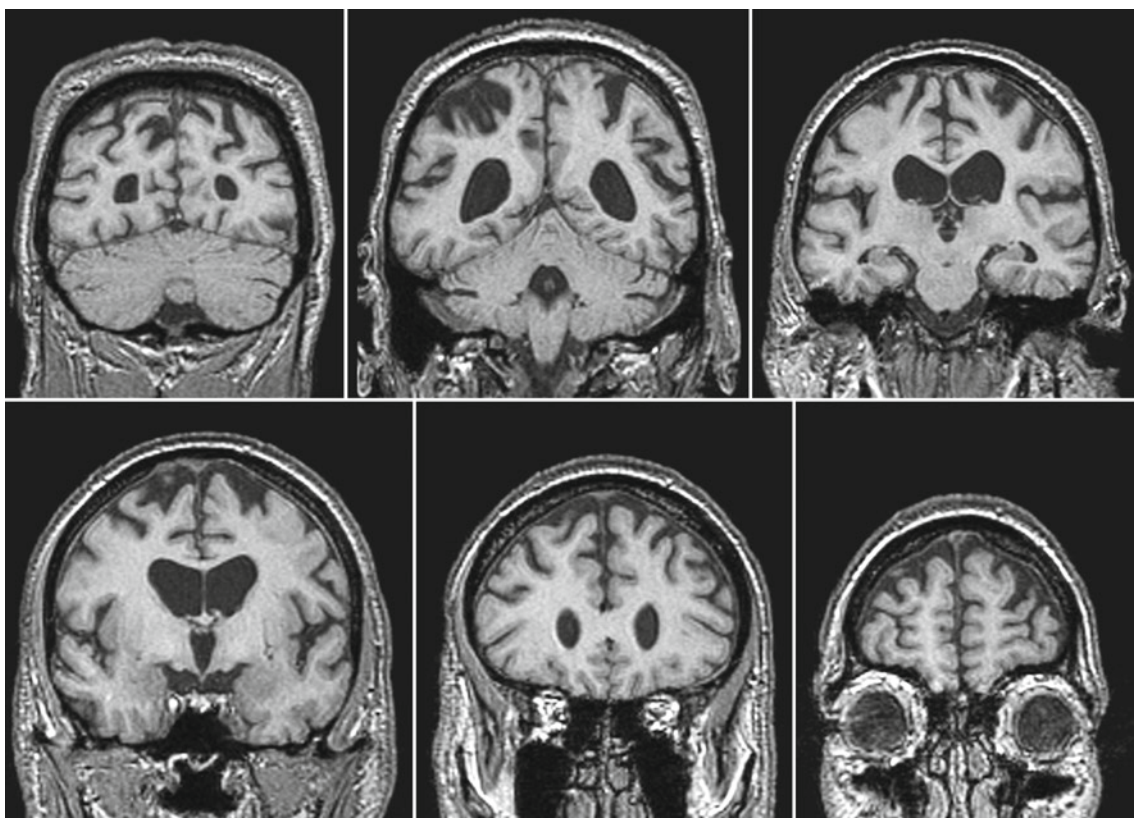


**Fig. 5.27** Corticobasal syndrome. Note superior frontal–parietal atrophy, with relatively little asymmetry in this case with confirmed tau-positive CBD pathology at post-mortem

#### 5.3.5.6 FTD with Motor-Neuron Disease (MND)

The association of MND with FTLD associates most commonly with bvFTD but also with PNFA. Patients may present initially with just fasciculations but often proceed to amyotrophy with involvement of upper and lower motor neurones later in the illness. Imaging studies are limited but suggest that FTD-MND is associated with relatively symmetrical prefrontal and medial temporal lobe atrophy.

#### 5.3.5.7 'Right Temporal Lobe Variant' of FTLD

Rarely, patients may present with a progressive neurodegenerative disorder in which symptoms are attributed to right temporal lobe atrophy, in particular prosopagnosia. It remains unclear, however, whether this is a distinct clinical syndrome. Although some of these patients subsequently develop the clinical syndrome of semantic dementia (with concomitant left temporal lobe atrophy) and similarly have FTLD-TDP pathology, others do not. Further clinical and particularly pathological characterization is required to further the nosological status of the right temporal lobe variant (Fig. 5.28a and b).

#### 5.3.5.8 Genetic Subgroups

*GRN* mutations have been described to be associated with strikingly asymmetrical atrophy of either cerebral hemisphere. Furthermore, unlike most other cases of

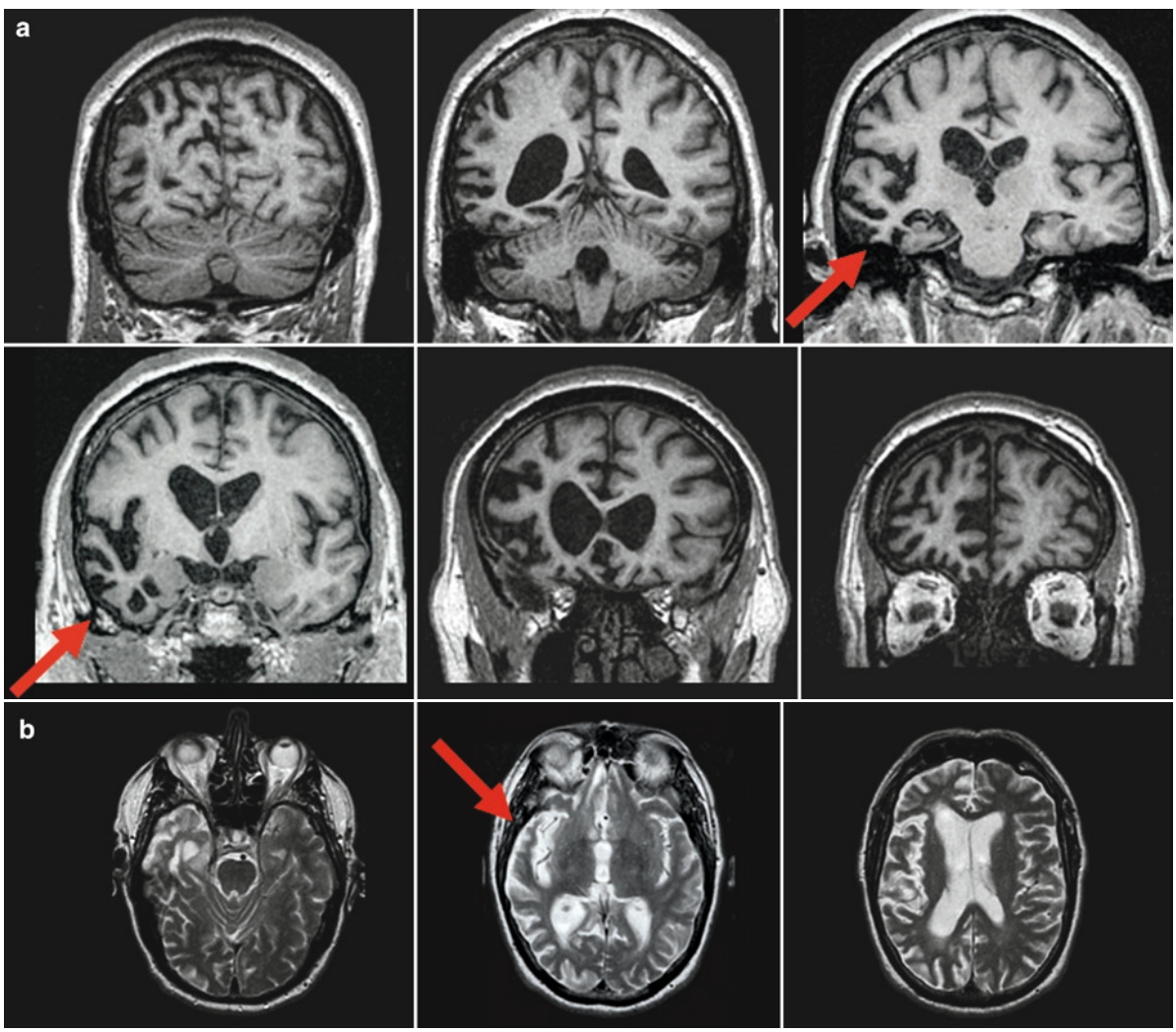



**Fig. 5.28** Right temporal lobe variant. Note severe atrophy (*red arrows*) of the right temporal lobe (lateral more than medial), with associated asymmetric frontal lobe atrophy

FTLD, early parietal lobe involvement is described. *MAPT* mutations are associated with frontotemporal atrophy with an antero-posterior gradient. Atrophy is commonly bilateral and is usually relatively symmetrical or only mildly asymmetrical (Fig. 5.29a and b).

### 5.3.6 Differential Diagnosis, Imaging Follow-up (Including PET/SPECT), Other Tests (CSF/EEG)

#### 5.3.6.1 Other Imaging

Functional imaging may be useful in FTLD (exemplified by the fact that reimbursement for PET scanning in permitted in the USA if FTLD is being considered). FDG-PET and (HMPAO-)SPECT characteristically show frontal and temporal hypoperfusion/hypometabolism with relative sparing of parietal and occipital blood flow in comparison with AD where posterior changes are more prominent. A pattern of bilateral frontal hypoperfusion in the absence of bilateral parietal hypoperfusion has been reported to have a sensitivity and specificity of 0.8 for a diagnosis of FTD. It can be useful particularly in separating patients who have a behavioural syndrome due to either FTLD or AD pathology. Little is known about the use of PET/SPECT in PNFA or SD – absence of hypoperfusion of temporo-parietal association cortex favouring FTLD over AD, but unilateral hypoperfusion may be associated with either type of pathology. SPECT findings in SD have not been studied in detail. As an alternative strategy, perfusion MRI may demonstrate hypoperfusion in temporal or frontal regions (Fig. 5.30).

$^{11}$C-PIB PET imaging is designed to specifically image amyloid plaques. Although it is yet to enter clinical practice, most studies have shown a high specificity for AD, with mostly negative scans in FTLD (Fig. 5.31 and 5.32). Amyloid imaging may become important in patients presenting with progressive aphasia when it is important to distinguish patients with likely Alzheimer pathology for management decisions – most commonly positive amyloid imaging is associated with LPA and only very rarely with PNFA or SD.

The use of magnetic resonance spectroscopy in FTLD is of limited value. N-acetylaspartate (NAA)/creatine (Cr) levels, a marker of neuronal loss, are lower in FTLD compared to controls but similar to Alzheimer's disease, mostly regional, occurring in the frontal and temporal but not the parietal lobes (Fig. 5.33). Myoinositol (mI)/Cr levels, a marker of gliosis, are higher than controls but again similar to Alzheimer's disease.

#### 5.3.6.2 CSF

Traditional CSF constituents are generally normal or negative i.e. white cell count, protein, glucose and oligoclonal bands. Current CSF biomarkers are not very useful in making a positive diagnosis of FTLD. Total tau may be increased relative to controls but to a lower level than in AD, but may also be normal, reflecting the heterogeneous nature of FTLD. Aβ42 levels in FTLD may be low but not as low as in AD – with considerable overlap. Large autopsy-proven studies are needed to assess the utility of CSF in FTLD.

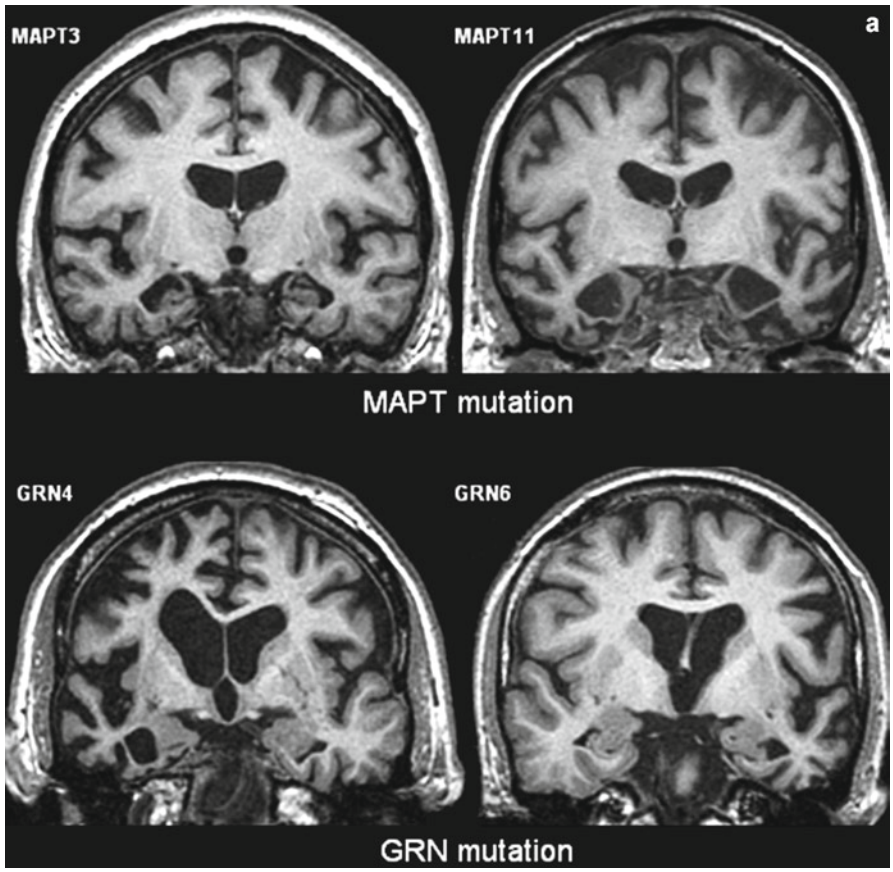
#### 5.3.6.3 EEG

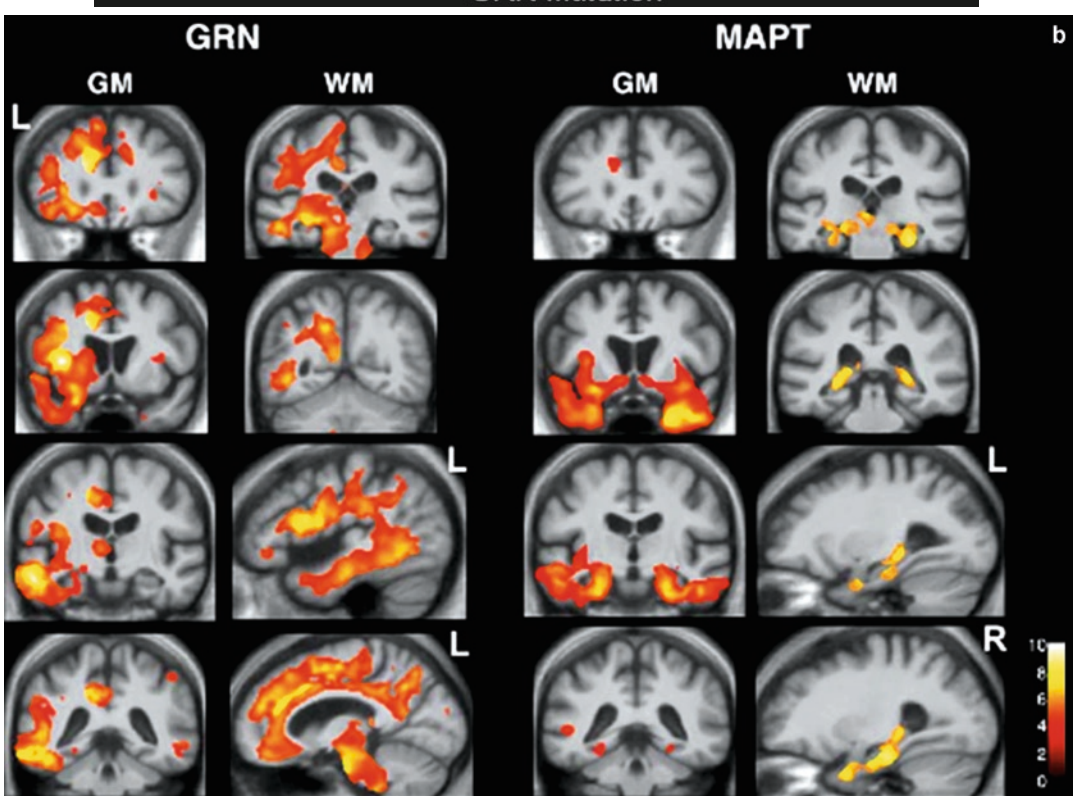
EEG in FTLD has traditionally been thought to be normal compared to the loss of alpha rhythm, generalized slowing and excess theta rhythm seen in AD. However, many patients in fact may have abnormal EEGs. Cases with a 'temporal' presentation (SD and right temporal lobe atrophy) are probably more likely to have an abnormal EEG compared to 'frontal' cases.

## 5.4 Dementia with Parkinsonism

### 5.4.1 Introduction: Neurodegeneration, Parkinsonism and Dementia

A number of neurodegenerative diseases present with a combination of cognitive impairment and parkinsonism (bradykinesia, rigidity, tremor and loss of postural reflexes) as prominent aspects of their phenotype. The degree and distribution of cognitive deficits varies according to the underlying pathological diagnosis, but a sub-cortical pattern of cognitive impairment is a common feature. The relative prominence and order of appearance of the parkinsonian features and the cognitive decline varies considerably between diseases. The balance between motor and cognitive deficits also varies within a specific disease and over time. Patients may be referred to movement disorders or to dementia


MAPT3
MAPT11
a
MAPT mutation
GRN4
GRN6
GRN mutation


GRN
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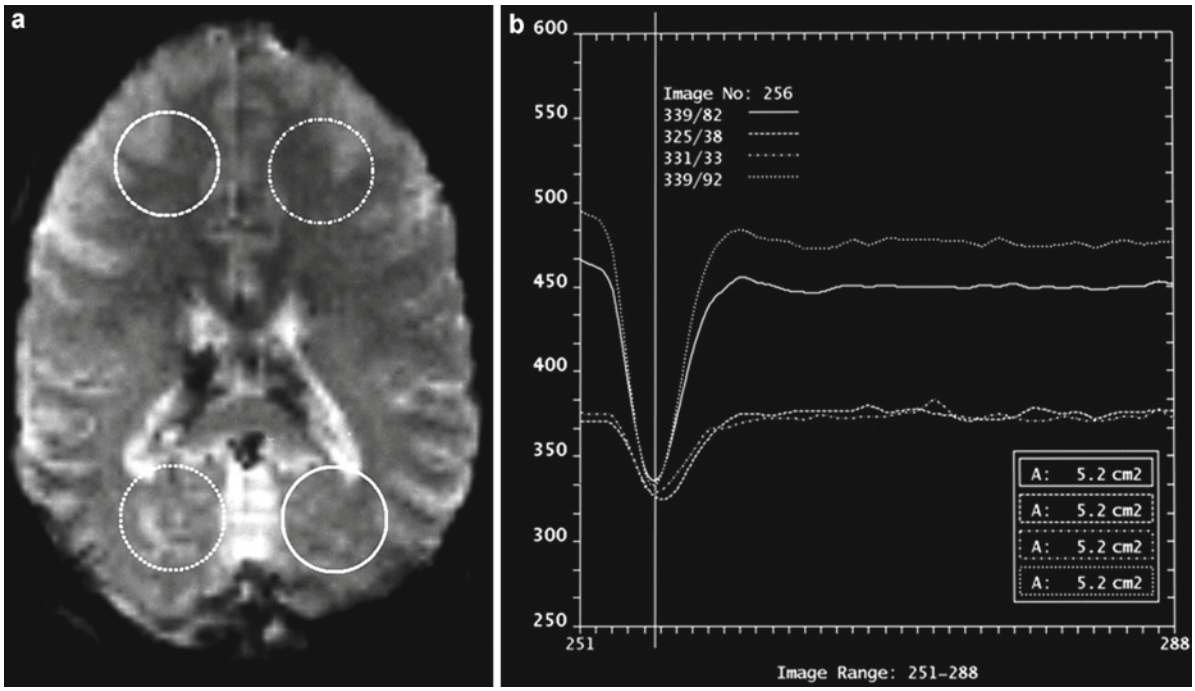



**Fig. 5.30** Perfusion MRI in FTD. MR perfusion study in a patient with probable frontotemporal dementia. (**a**) On the EPI image of the perfusion series the regions of interest are indicated: two in the frontal lobes and two in the occipital lobes. (**b**) The graphic analysis of the perfusion in these areas. It is clear that the perfusion in the frontal lobes is reduced to about one-third of the occipital perfusion. This finding supports the diagnosis of frontotemporal dementia

clinics – and fall into the 'parkinson's-plus' or the 'dementia-plus' diagnostic sieve depending on the specialism of the investigating physician. In many of these conditions, additional phenotypic features such as dysautonomia, gaze palsies, cerebellar and pyramidal signs may suggest one pathological process over another, but none are pathognomic. Histopathologically as well as phenotypically there is overlap with FTLD: e.g. progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are both tauopathies; see also Sect. 5.3.

Lewy body disorders are the most common causes of progressive cognitive decline with parkinsonism. Once considered separate entities, dementia with Lewy bodies (DLB) and Parkinson disease dementia (PDD) are now best thought of as ends of a continuous spectrum – the former with an initial presentation with dementia, the latter presenting with parkinsonism followed by dementia after more than a year but ultimately both have widely distributed Lewy bodies in the cerebral cortex. These disorders are therefore discussed together in the next section.

**Fig. 5.29** (**a**) Impact of genetic mutation on atrophy pattern. Two patients with MAPT mutations both presenting with behavioural variant frontotemporal dementia (*top*); two patients with progranulin mutations presenting with a progressive aphasia (predominant left hemisphere atrophy) and with behavioural variant frontotemporal dementia (predominant right hemisphere atrophy) – in both these progranulin cases the atrophy is very asymmetric. Note the wide dispersion of imaging phenotype by genotype. (**b**) Voxel-based morphometry studies in FTLD. VBM analysis on grey matter (GM) and white matter (WM) regions in GRN- and MAPT-associated FTLD relative to healthy controls. Statistical parametric maps (SPMs) have been thresholded at $p < 0.001$ after false discovery rate correction over the whole-brain volume and rendered on a study-specific average group T1-weighted MRI template image in DARTEL space. The colour bar (*lower right*) indicates the t score. *Left* (*L*) and *right* (*R*) markers are shown for ease of reference. GM panels show the same series of coronal MR sections in the GRN and MAPT cases; WM panels show coronal (*above*) and sagittal (*below*) sections based on zones of maximal white matter loss in each disease group

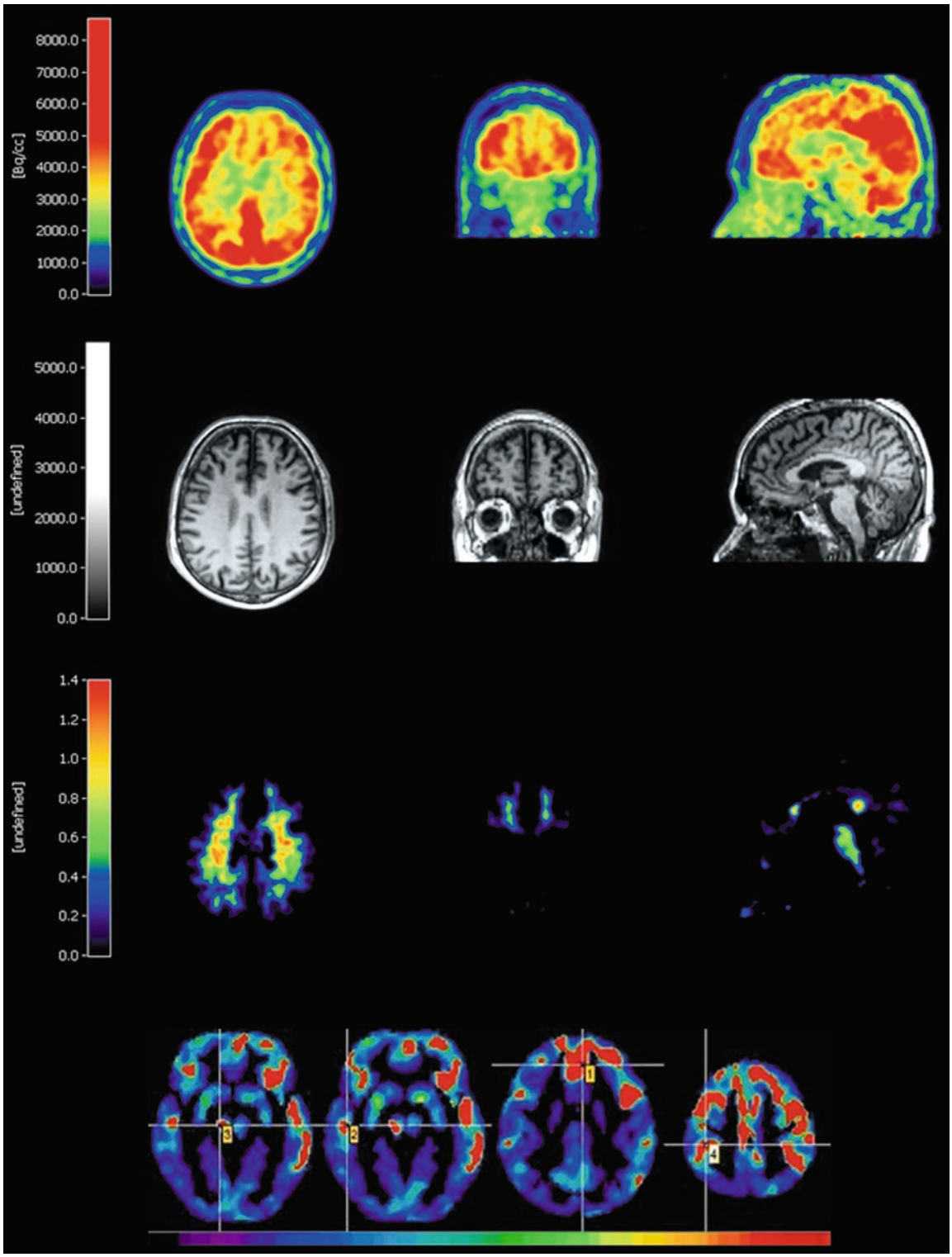



**Fig. 5.31** Behavioural variant FTD. This 68-year-old man with a psychiatric history presented with recent onset of altered behaviour and lack of initiative. There were no speech or language abnormalities. Co-registered FDG-PET (*upper row*) shows frontal hypometabolism and concomitant mild frontal atrophy on MRI (*second row*). Normal CSF findings and normal amyloid-PET (PIB, third row with only white matter, but no cortical uptake) ruled out AD. Note that the voxel-wise map of the FDG scan (*bottom row*) shows abnormal metabolism mostly in frontal areas, but not in the posterior cingulate, as in AD

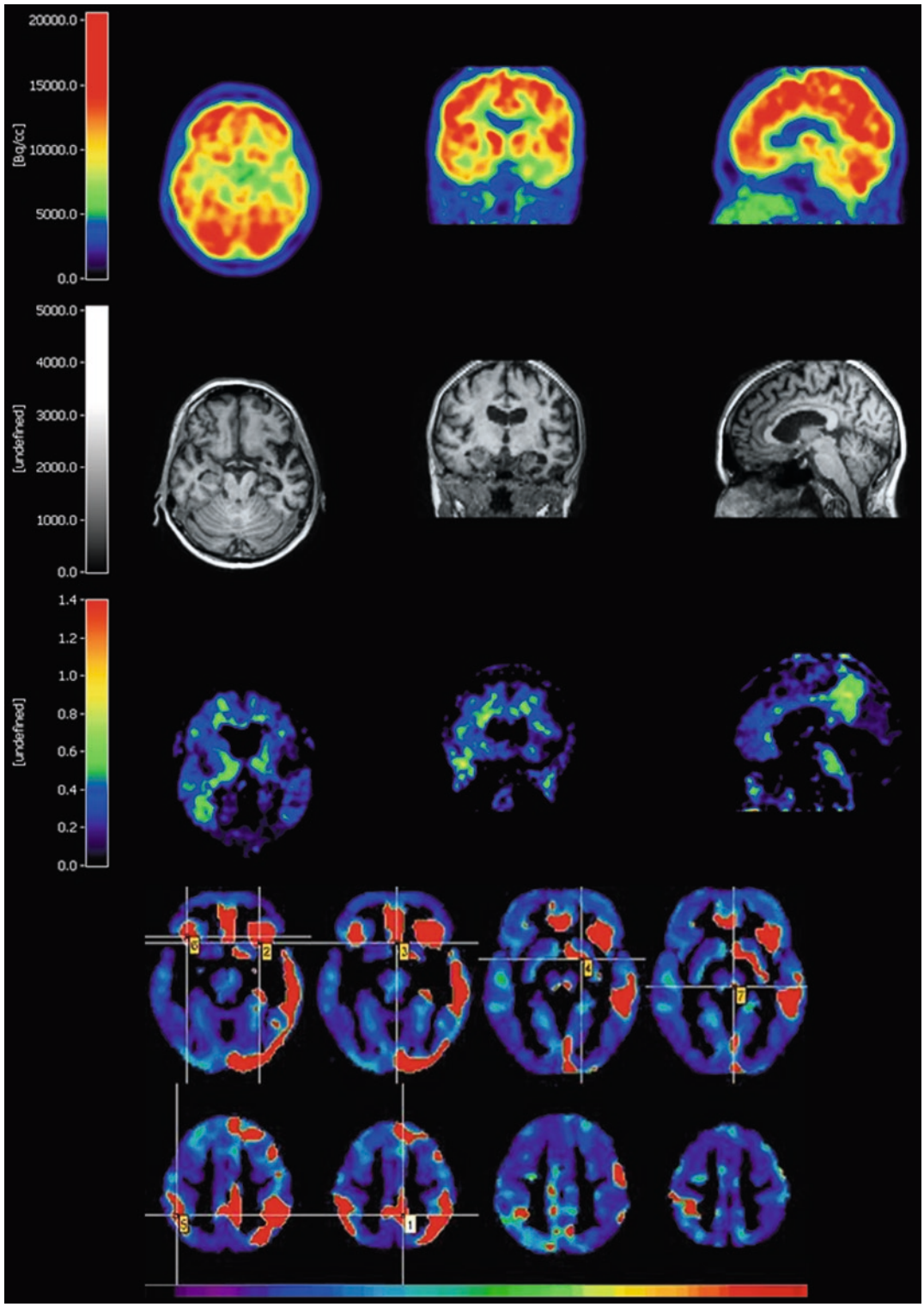



**Fig. 5.32** PET in semantic dementia. This 62-year-old woman presented with slowly progressive impaired word-finding which developed over the course of 1 year. Examination revealed anomia, fluent language and mild memory disturbances (MMSE 24/30). MRI showed marked left temporal pole atrophy. FDG-PET (*upper row*) also showed reduced temporal metabolism, and additional frontal hypometabolism (red areas on the voxel-wise map in *bottom panel*). Amyloid-PET (*third row*) showed hardly any cortical PIB-binding, ruling out atypical AD

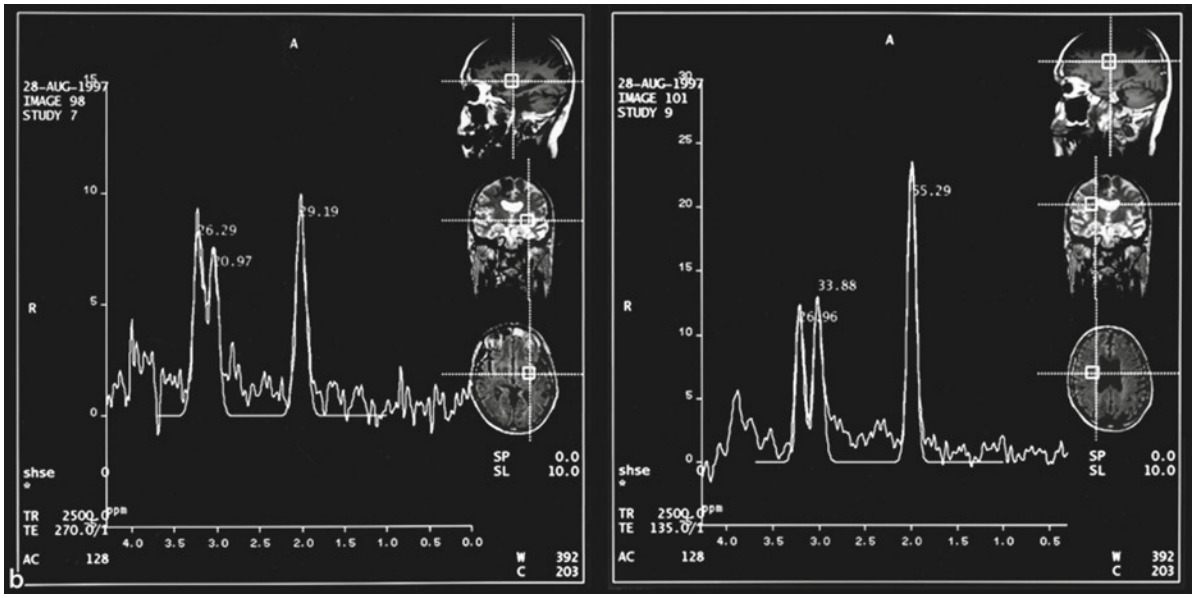



**Fig. 5.33** MR spectroscopy in FLTD. The spectrum of the left insular region (*left panel*), despite some broadening of the spectral lines, shows decreased N-acetylaspartate and some increase in choline. Lactate is not present. The spectrum of the right paraventricular region (*right panel*) is normal. Note that the two spectra were not corrected for signal intensities as displayed along the x-axis

## 5.4.2 Dementia with Lewy Bodies and Parkinson's Disease Dementia

*John O'Brien and Michael Firbank*

**Synonyms**

Dementia with Lewy bodies (DLB); Diffuse Lewy body disease; Dementia associated with cortical Lewy bodies; The Lewy-body variant of Alzheimer's disease; Lewy body dementia; Senile dementia of Lewy-body type; Parkinson's disease dementia (PDD);

### 5.4.2.1 History and Nosology

Lewy bodies (LB) are spherical, neuronal inclusions that were first described by the German neuropathologist Friedrich Lewy in 1912, examining cases of 'paralysis agitans'. In 1961, a case report was published about two elderly men who presented with dementia and died shortly thereafter with severe extrapyramidal rigidity. Autopsy showed LB in their cerebral cortex. Over the next 20 years, Japanese researchers reported a further 34 similar cases. Lewy body disease thus came to be considered as a rare cause of dementia until a series of studies in Europe and North America in the late 1980s identified LB in the brains of 15–20% of elderly demented cases reaching autopsy, establishing it as a common form of degenerative dementia in old age. Dementia with Lewy bodies (DLB) is now the preferred term for such cases. Its recent recognition is largely due to the widespread use of improved neuropathological techniques that enhance visualization of cortical LB, in particular anti-ubiquitin immunocytochemistry. DLB is responsible for around 15% of cases of late-onset dementia and is therefore the second most common degenerative dementia in the elderly after AD.

Parkinson's disease (PD) is a major risk factor for dementia. Parkinson's disease dementia (PDD) has a prevalence of 20–30% among PD subjects, but detailed longitudinal studies have shown that the majority of PD subjects will develop PDD if they live long enough and that age is a major risk factor for the development of dementia in PD. PDD and DLB share cognitive, neuropsychiatric, neurochemical, pathological and imaging similarities, suggesting they should be considered the same disorder or different ends of the same spectrum. The distinction between DLB and PDD is based on the sequence of symptom appearance. If parkinsonism precedes dementia by <1 year, or follows the dementia, the diagnosis is

DLB. If dementia develops >1 year after parkinsonism, then PDD is used. The clinical and cognitive features of PDD are similar to DLB; parkinsonism is (by definition) invariably present in PDD, while both fluctuation and visual hallucinations are slightly less frequent than in DLB. While arbitrary, this distinction allows a common definition to facilitate research into the boundaries between the two.

#### 5.4.2.2 Clinical Findings and Treatment

Clinically, the characteristic features that distinguish DLB from AD include fluctuating cognitive impairment, prominent (vivid) and recurrent visual hallucinations and spontaneous extrapyramidal symptoms. Other important features are neuroleptic (antipsychotics) hypersensitivity and REM sleep-behaviour disorder. According to the current International Consensus Criteria, the diagnosis of DLB requires at least two of these three features (Table 5.9).

Men appear to be more susceptible to DLB than women. The extrapyramidal features are typically bilateral and include rigidity, bradykinesia, mask-like facies, stooped posture, and a slow, shuffling gait. In many patients the only parkinsonian sign is an abnormal gait. Resting tremor is less common. The extrapyramidal features typically show modest response to anti-parkinson treatments. The visual hallucinations are typically recurrent and detailed and may involve people and animals. The visual hallucinations most reliably distinguish the disorder clinically from AD or

**Table 5.9** Consensus criteria for the clinical diagnosis of *probable* and *possible* dementia with Lewy bodies (DLB)

| |
|---|
| 1. The *central feature* required for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of executive function, and visuospatial ability may be especially prominent. |
| 2. Two of the following *core features* are sufficient for a diagnosis of probable DLB, one is sufficient for possible DLB<br>(a) Fluctuating cognition with pronounced variations in attention and alertness<br>(b) Recurrent visual hallucinations which are typically well formed and detailed<br>(c) Spontaneous features of parkinsonism |
| 3. Features *suggestive* of the diagnosis. If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.<br>(a) REM sleep behaviour disorder<br>(b) Severe neuroleptic sensitivity<br>(c) Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging |
| 4. Features *supportive* of the diagnosis (which are commonly present, but not proved to have diagnostic specificity)<br>(a) Repeated falls and syncope<br>(b) Transient, unexplained loss of consciousness<br>(c) Severe autonomic dysfunction e.g. orthostatic hypotension, urinary incontinence<br>(d) Systematized delusions<br>(e) Depression<br>(f) Hallucinations in other modalities<br>(g) Relative preservation of medial temporal lobe structures on CT/MRI scan<br>(h) Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity<br>(i) Abnormal (low uptake) MIBG myocardial scintigraphy<br>(j) Prominent slow wave activity on EEG with temporal lobe transient sharp waves |
| 5. A diagnosis of DLB is *less likely*<br>(a) In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging<br>(b) In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture<br>(c) If parkinsonism only appears for the first time at a stage of severe dementia |
| 6. *Temporal sequence*<br>DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term Parkinson's disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson's disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. |

*Source:* McKeith et al. (2005) Neurology 65;1863–1872

vascular dementia (VaD). Although hallucinations and delusions occur in AD, visual hallucinations occur in 80% of patients with DLB; 45% have auditory hallucinations, 9% have delusions. Depression is more common than in AD. Recognition of the disorder is particularly important because of the potentially dangerous adverse reaction to neuroleptics.

Treatment of DLB is symptomatic only. Overall, patients with PDD and DLB respond to cholinesterase inhibitors (AChEI) at least as well as patients with AD. Hallucinations in particular can often be very responsive to AChEI treatment. The benefit of memantine in DLB is less clear with some reports of improvement in attention but also worsening of delusions.

#### 5.4.2.3 Neuropathology, Aetiology and Genetics

Macroscopically, the brain of a patient with DLB has less cortical and less hippocampal atrophy than the brain of a patient with AD with a similar level of dementia severity. In addition to the presence of Lewy bodies (which may also be present in AD), the pathological feature that distinguishes DLB from AD is the presence of ubiquitin-positive neurites in the CA2–CA3 region of the hippocampus. Prominent neurofibrillary tangles in the cortex are absent. Psychiatric symptoms are reflected in the prominent involvement of the limbic system: amygdala, limbic cerebral cortex, including the cingulate, entorhinal and temporal cortex. Extra-pyramidal features are due to the involvement of the substantia nigra. Dysphagia is caused by the involvement of the dorsal motor nucleus; autonomic dysfunction is the result of the involvement of the intermedio-lateral cell column and the sympathetic ganglia.

Neurochemically, DLB is characterized by alpha-synuclein, a presynaptic protein with unknown function. In DLB, a cholinergic deficit exists greater than in AD, possibly explaining the beneficial response to cholinesterase inhibitors. Similar findings are reported in PDD, though PDD has been associated with greater nigrostriatal loss than DLB, and DLB with greater cortical pathological burden of both Alzheimer and synuclein pathology.

Familial forms of DLB have been reported, but typically the disease occurs in a sporadic fashion and no known genetic mutations exist. In line with this, the aetiology of Lewy body pathology remains elusive.

#### 5.4.2.4 Neuroimaging Strategy

Neuroimaging findings are similar in DLB and PDD; so both are considered here together. Structural imaging can be used to rule out vascular disease as the cause of Parkinsonism, and also to render a diagnosis of AD less likely (absence of medial temporal lobe atrophy). Molecular imaging (SPECT/PET of dopamine transporter uptake) has greater specificity for DLB/PDD and is most helpful in the differential diagnosis with AD. The imaging findings are summarized in Table 5.10.

##### MRI Findings

Anatomical T1-weighted MR in DLB/PDD most consistently found that in the medial temporal lobe, there is less atrophy in DLB/PDD than AD on visual inspection – best assessed on thin slice coronal imaging (see

**Table 5.10** Neuroimaging findings in DLB/PDD

| |
|---|
| Atrophy pattern<br>• Mild generalized atrophy, with no specific predilection<br>– Atrophy rates lower than in AD<br>– Severe occipital atrophy more likely in Balint variant of AD<br>• Hippocampal atrophy initially mild/absent<br>– Prominent in late-onset AD, but may be absent in presenile AD<br>• Mild midbrain atrophy only |
| Vascular white matter lesions<br>• Slightly more than in normal ageing<br>– Extensive lesions may suggest vascular dementia |
| Cerebral blood flow and metabolism<br>• General reduction, most marked in occipital region<br>– Quite similar to AD<br>• Focal deficits favour vascular dementia rather than DLB |
| Dopaminergic imaging – most important marker<br>• Abnormal striatal uptake<br>– Putaminal before caudate abnormality<br>– May be asymmetric initially |
| Amyloid imaging<br>• Cortical uptake may be similar to AD |
| Differential diagnosis and red flags<br>• AD – severe hippocampal/precuneus atrophy early in disease<br>• PSP – humming bird sign (mesencephalon)<br>• MSA – ‘cross sign’ or pontine atrophy<br>• Vascular dementia – severe white matter lesions, lacunes, infarcts<br>– may have brain stem involvement |

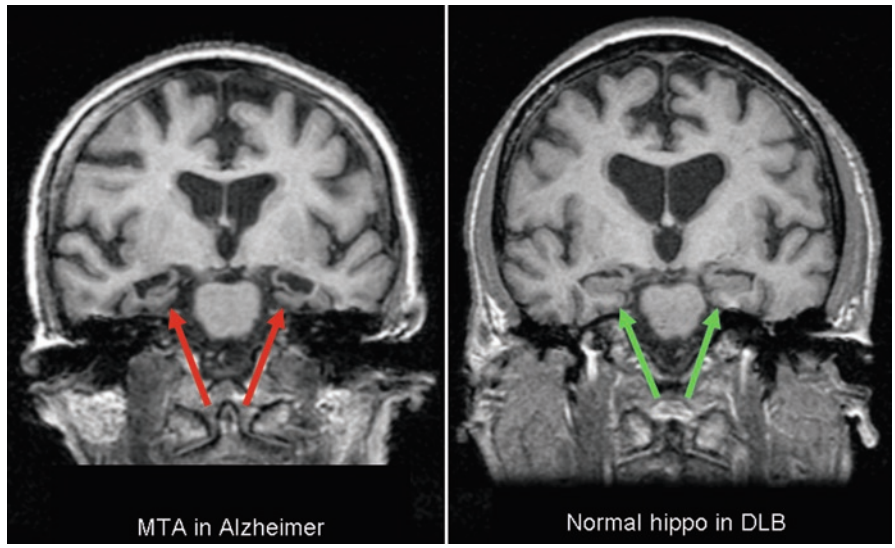



**Fig. 5.34** Medial temporal lobe appearance in DLB versus AD. Coronal T1-weighted MRI in an Alzheimer patient (*left*) shows marked medial temporal atrophy (MTA: *red arrows*). Note normal hippocampi (*green arrows*) in DLB patient on the *right*

Fig. 5.34) or on volumetric analysis. However, this is a matter of degree which needs to take into account the severity of the patient – medial temporal atrophy does not rule out a diagnosis of DLB since it will become prominent in more severe disease and older patients. In fact, atrophy of the hippocampus is related to Alzheimer-type pathology in both disorders.

Voxel-based methods show increased atrophy in DLB/PDD relative to controls (see Fig. 5.35) in insular cortex, frontal, inferior parietal & temporal lobes, with relative sparing of the sensory-motor cortex; some studies found little cortical atrophy in DLB, with only changes in the midbrain region. In the midbrain, substantia innominata atrophy has also been reported in DLB, though midbrain changes can be found in AD as well. Putaminal volume reduction (of about 15%) has also been observed in DLB and advanced PD, which may be a result of increased striatal synuclein pathology.

Longitudinal rates of whole brain atrophy in PDD/DLB are probably intermediate between healthy ageing and AD. The atrophy rates in DLB and PDD are probably similar, and vary with disease duration. In summary, atrophy is widespread but modest in DLB/PDD, with *initially* preserved medial temporal lobes in comparison to (incipient) AD.

White matter hyperintensities on T2-weighted images are perhaps more severe in DLB/PDD than healthy subjects, but no more so than in AD. They probably reflect concomitant vascular problems. However, evidence of extensive cerebrovascular pathology (stroke, severe white matter lesions) makes the diagnosis of DLB less likely (Tables 5.9 and 5.10).

The few studies using MR spectroscopy have found less change than in AD, with relatively normal NAA and myo-inositol levels. Using fMRI, one study in DLB found reduced activity in response to moving stimuli. Studies of Parkinson's disease with hallucinations have found reduced cortical responsivity to visual stimuli.

## PET/SPECT Findings

### *Perfusion/Metabolism*

FDG-PET and SPECT using a variety of tracers ($^{99m}$Tc-HMPAO, $^{123}$I-IMP and $^{99m}$Tc-ECD) show a similar pattern of hypometabolism/perfusion in DLB and PDD particularly involving occipital cortex, midline and inferior parietal regions, lateral temporal cortex, inferior and medial frontal lobe (Fig. 5.36). In comparison to AD there is lower occipital metabolism in DLB/PDD (Fig. 5.37). Focal hypometabolism/perfusion is indicative of stroke/cerebrovascular disease, and hence makes the diagnosis of DLB/PDD less likely.

### *Dopaminergic System*

The $^{123}$I labelled dopaminergic presynaptic ligand FP-CIT has been extensively studied in PDD/DLB. In

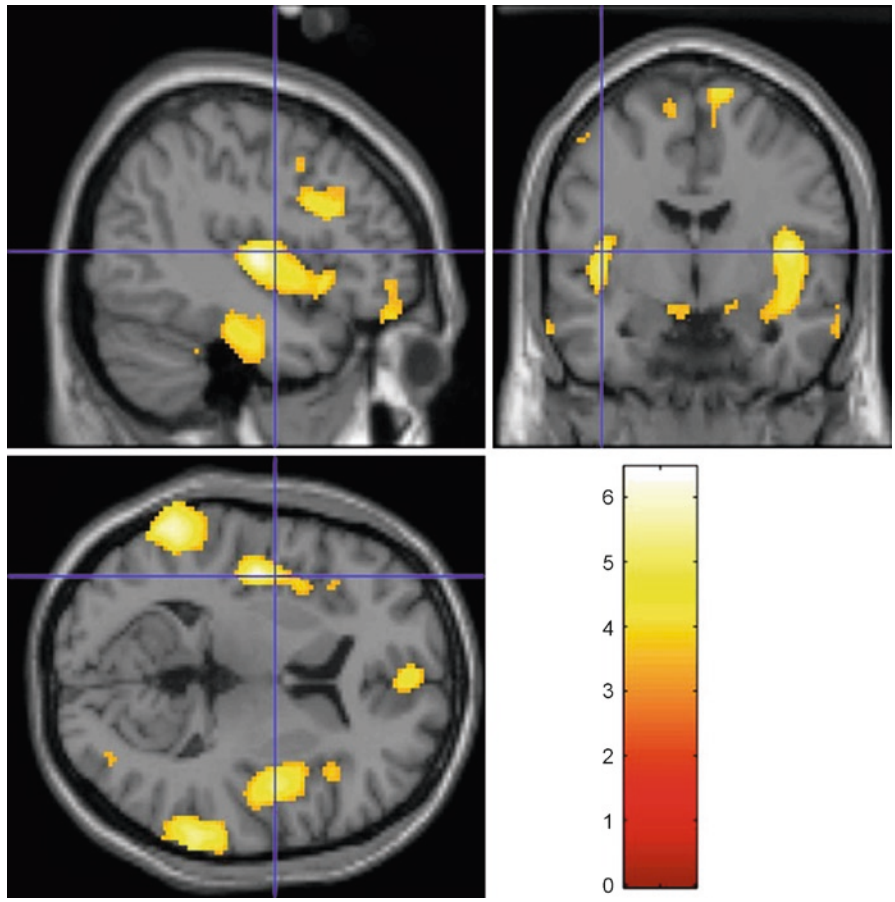



**Fig. 5.35** Grey matter atrophy in DLB. Voxel-wise mapping of grey matter loss on MRI in DLB relative to healthy control subjects of similar age

normal subjects and those with AD, the ligand is taken up in the caudate and putamen, whereas in PDD and DLB uptake is almost absent in the putamen, and reduced in the caudate (Fig. 5.38). Abnormal FP-CIT imaging has good diagnostic accuracy for DLB/PDD with sensitivity ~75% and specificity of ~90% for distinguishing PDD/DLB from non-DLB dementia (e.g. AD). PDD is associated with more pronounced overall striatal dopaminergic striatal loss than DLB, consistent with autopsy findings of greater nigrostriatal dopaminergic cell loss.

### *Amyloid Imaging*

PET imaging with the $^{11}$C-labelled Pittsburgh Compound B (PIB) is positive (suggesting amyloid deposition) and appears similar to AD in 40–80% of subjects with DLB (less so in PDD).

### *Cardiac Imaging*

Cardiac scintigraphy using iodine-123 meta-iodobenzylguanidine ($^{123}$I-MIBG), an analogue of noradrenaline, has been used for estimating local myocardial sympathetic nerve damage. The ratio of uptake in heart to mediastinum uptake is calculated using a region of interest. This ratio has been found to be reduced in DLB and PDD in comparison to AD and healthy subjects with a diagnostic accuracy for DLB/PDD vs. AD of approximately 90% though currently, studies with larger group sizes are needed to confirm the diagnostic accuracy.

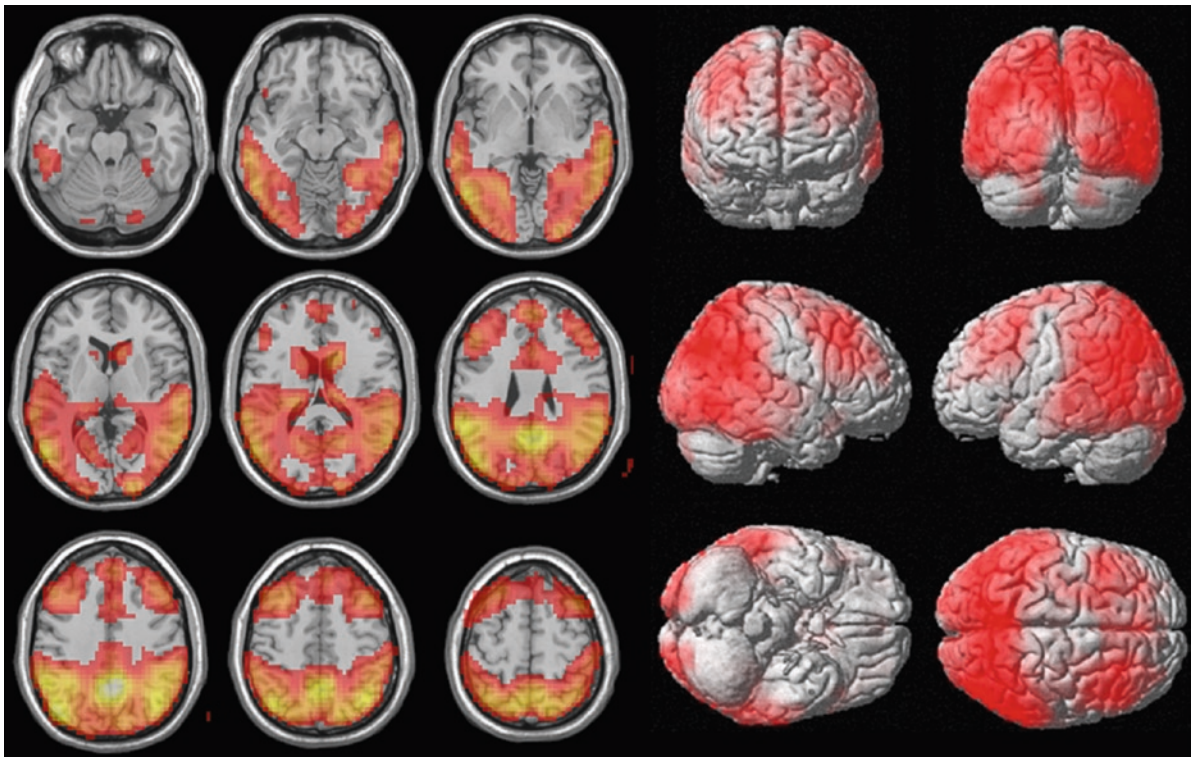


**Fig. 5.36** Hypoperfusion in DLB/PDD. Voxel-wise analysis (from HMPAO-SPECT) of DLB/PDD group versus healthy controls. Regions of reduced perfusion are overlaid in *red/yellow* onto a standard MRI anatomical scan on the *left*; surface rendering on the *right*

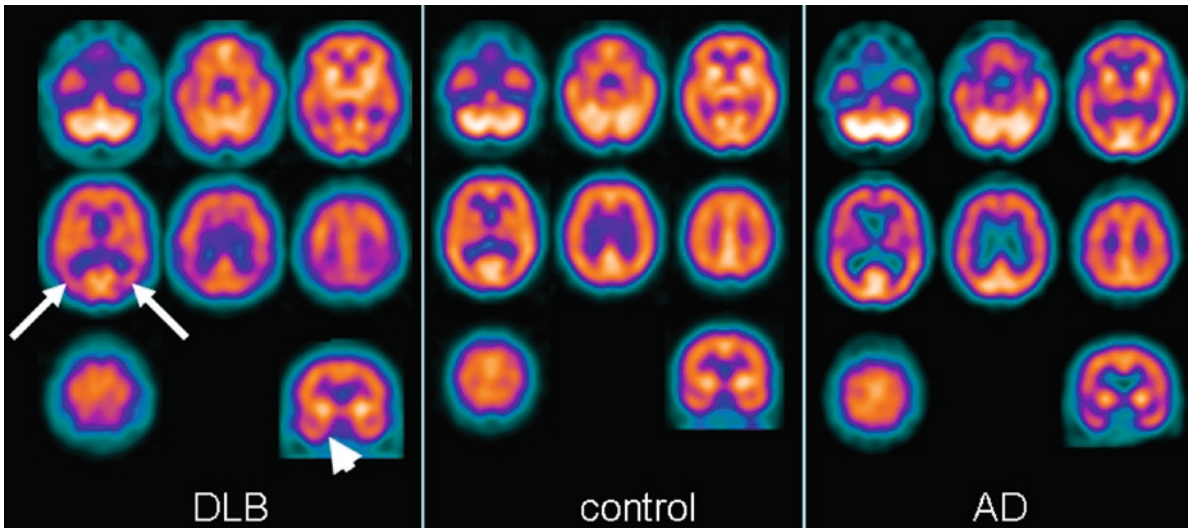



**Fig. 5.37** Hypoperfusion in DLB versus AD. Axial slices HMPAO SPECT scan of DLB subject (*left*), healthy control (*middle*) and AD patient (*right*). Bottom right image in each panel is a coronal section through the medial temporal lobe. Note low signal in occipital lobe (*arrows*) and preserved medial temporal lobe (*arrow head*) in DLB

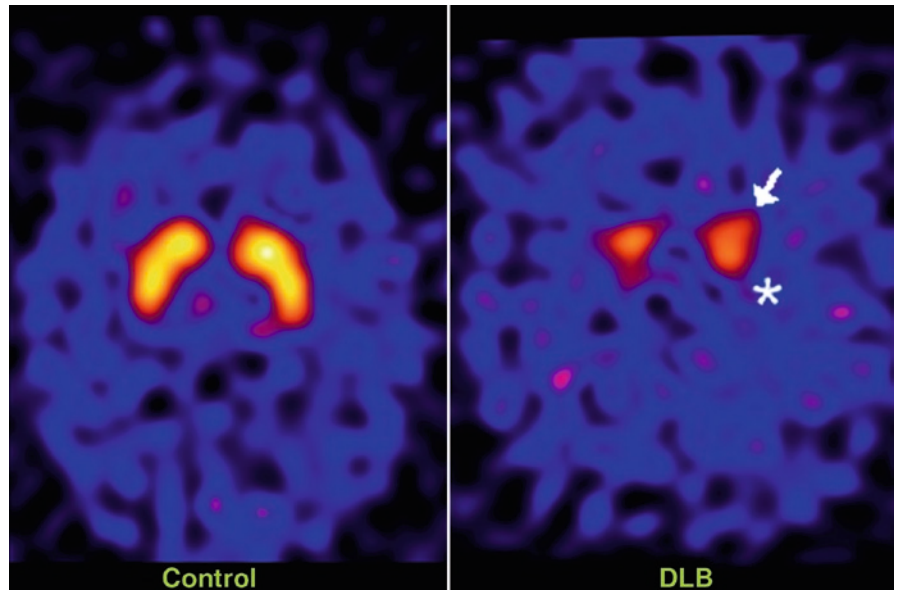



**Fig. 5.38** Dopaminergic imaging in DLB. Axial images from FP-CIT scan of control and DLB subject showing reduced dopamine transporter density in the caudate (*arrow*) and putamen (*asterisk*)

#### 5.4.2.5 Differential Diagnosis and Imaging Follow-up

No sensitive or specific blood, cerebrospinal fluid (CSF), or urine tests are currently available for DLB. In a typical case, there may be limited need for anything more than structural (MR) imaging. However, the differential diagnosis in DLB/PDD is wide and atypical cases are common. The differential may be divided into two broad categories: First, where cognitive decline is the prominent feature and with some parkinsonism. In this situation the differential relates to DLB versus AD +/– VaD. The second category is distinguishing DLB/PDD from atypical parkinsonian syndromes which includes PSP, CBD, MSA and FTLD. The key imaging modalities are a combination of MRI to assess hippocampal atrophy (AD versus DLB); focal fronto-temporal atrophy (FTLD, CBD), midbrain atrophy (PSP), pontine/cerebellar atrophy (MSA) and vascular load; and dopamine transporter imaging to assess the dopaminergic deficit.

### 5.4.3 Progressive Supranuclear Palsy (PSP)

*Dominic Paviour*

**Synonyms**

Steele-Richardson-Olszewskisyndrome;Richardson's syndrome; PSP-P;

#### 5.4.3.1 History

In June 1963, Dr Clifford Richardson presented a clinical report of eight cases collected over approximately ten years, of 'heterogenous system degeneration' with supranuclear ophthalmoplegia, pseudobulbar palsy, nuchal dystonia and dementia. He described a previously unrecognized disorder occurring in the seventh and eighth decades of life which progressed to death occurring within 9 years. The following year, together with Dr John Steele, they published a seminal paper entitled 'Progressive supranuclear palsy'.

#### 5.4.3.2 Clinical Presentation

When the typical features of PSP are present, it provides a striking clinical picture. Patients often present with falls, typically backwards, as well as mild symmetrical Parkinsonism. The classic supranuclear ophthalmoplegia results initially in slowed vertical saccades and progresses through impaired vertical and horizontal pursuit movements (correcting with vestibulo-ocular reflexes) to a complete ophthalmoparesis. Axial rigidity is a striking feature of the typical clinical syndrome resulting in an upright posture and a 'growling' dysarthria is frequently described.

Atypical clinical presentations of PSP include so-called PSP-Parkinsonism cases present with asymmetric Parkinsonism and tremor with the ophthalmoplegia

occurring later. This is distinct from the more typical Richardson's syndrome.

Cases presenting with pure akinesia without rigidity, gait freezing, rest tremor, isolated dementia, parkinsonism without dementia, limb apraxia and asymmetric parkinsonism as well as a number of cases dying without recorded evidence of the distinctive supranuclear ophthalmoplegia have been reported.

Despite these observations, the current operational criteria for the diagnosis of PSP include very few clinical features that were not recognized in the original description. The high specificity of these criteria is important for clinical research studies, but their sensitivity is suboptimal for clinical care and descriptive epidemiological studies. Patients are generally considered as 'clinically possible' PSP if they suffer from a gradually progressive disorder of more than 12 months duration, with age at onset after 40 years, and with a tendency to fall within the first year of disease onset, in the absence of defined exclusion criteria Table 5.11. There should be no clinical features suggestive of Creutzfeldt–Jakob disease or any other identifiable cause for their postural instability.

In terms of prognosis, the absence of supranuclear gaze palsy, early falls and early bulbar dysfunction, with a positive response to levodopa, convey a better prognosis. There are no definite biological markers for the ante-mortem diagnosis of PSP and the 'definite' diagnostic category has traditionally been reserved for cases that are pathologically confirmed. The cases that remain undiagnosed in life make up at least 20% of the pathologically diagnosed cases of PSP and most have unusual or atypical clinical pictures. There is no specific treatment for PSP.

#### 5.4.3.3 Neuropathology and Genetics

Like FTLD, PSP is a tauopathy (see Sect. 5.3). Tau is a microtubule-associated protein, which in the normal human brain is distributed mainly in axons. By supporting cytoskeletal structure and sustaining axonal transport, tau plays a fundamental role in neuronal survival. In normal neurones, tau is soluble, binds to microtubules reversibly and has a rapid turnover. In neurodegenerative diseases such as PSP, tau loses its affinity for microtubules and collects as insoluble aggregates in the form of proteolytic resistant filaments.

PSP is characterised by the presence of neurofibrilliary tangles (NFTs) and neuropil threads (NTs) resulting from aggregation of hyperphosphorylated tau protein filaments. The NFTs are basophilic and globose, their structure resembling a ball of string. However, flame-s haped tangles (characteristic of AD) can also occur in PSP.

The pathological criteria for the diagnosis of PSP are well established and reflect many of the findings described by Olszewski, specifically neuronal loss with gliosis and NFTs in the subcortical and brainstem nuclei and the cerebellar dentate nucleus. New immuno-histochemical methods have allowed further characterization of the pathological changes and some

**Table 5.11** NINDS-SPSP Diagnostic criteria for PSP (after Litvan et al. 1996)

| Diagnostic categories | Inclusion criteria | Exclusion criteria | Supportive criteria |
|---|---|---|---|
| *For possible and probable:* | *For possible and probable:* | *For possible and probable:* | Symmetric akinesia/rigidity, retrocollis; poor/absent response to levodopa; early dysphagia & dysarthria; early onset of cognitive impairment including > 2 of: apathy, impaired abstract thought, decreased verbal fluency, utilization or imitation behaviour, or frontal release signs |
| | Gradually progressive disorder with age at onset at 40 or later; | Encephalitis; alien limb; cortical sensory deficits; hallucinations or delusions unrelated to dopaminergic therapy; prominent, early cerebellar symptoms or unexplained dysautonomia | |
| Possible | Either vertical supranuclear palsy or both slowing of vertical saccades & postural instability with falls <1 year disease onset | | |
| Probable | Vertical supranuclear palsy and prominent postural instability with falls within first year of disease onset | | |
| Definite | All criteria for possible or probable PSP are met and histopathologic confirmation at autopsy | | |

regional pathological variation has been reported. The characteristics of the pathological accumulation of the microtubule protein tau into filamentous deposits of abnormally phosphorylated protein have also been examined in PSP. Alternative splicing of the tau gene transcript from Chromosome 17 yields six different tau isoforms. The selective tau deposition in clinically and pathologically distinct diseases differs by the relative amounts of tau containing three (3R-tau) or four (4R-tau) microtubule-binding domains. Normal brain has 3R-tau isoforms; in PSP, hyper-phosphorylated 4R-tau is abundant (Fig. 5.18).

Braak has postulated that in idiopathic Parkinson's disease, the pathology begins in the lower brainstem structures and spreads caudally to involve progressively upper brainstem structures and eventually the neo-cortex. This theory does not explain the diversity in disease presentation whereby as an example patients may present with predominant tremor or with much more prominent bradykinesia or even cognitive disturbances. Whether a similar topographic evolution of the pathology occurs in PSP and other tauopathies is not clear; however, in typical PSP, or Richardson's syndrome, the brainstem is likely to be involved earlier than cortical sites.

#### 5.4.3.4 Neuroimaging Findings

MRI and CT may show generalized supratentorial atrophy in PSP, sometimes with a frontal predominance. Most importantly, however, MRI allows better visualisation of the posterior fossa and brainstem structures on sagittal images and is helpful to discriminate 'atypical Parkinsonism' (including PSP and MSA) from PD.

The characteristic qualitative imaging features of PSP include midbrain atrophy, divergence of the red nuclei, dilatation of the third ventricle, atrophy of the superior cerebellar peduncle and frontal cortical atrophy. The term 'hummingbird' is used to describe the midsagittal imaging appearance (Fig. 5.39), while the axial appearance has been referred to as the 'Mickey Mouse' sign; more detailed information is provided in Table 5.12.

Definitive and diagnostically supportive abnormalities may only be seen in about 50% of patients with a clinical diagnosis of PSP and clear MRI abnormalities are more likely to be present in individuals with typical clinical presentations and as it is the atypical cases that need diagnostic clarification, the MRI appearances may only help to reinforce the existing clinical diagnosis rather than dispelling diagnostic uncertainty.

In addition to the brainstem nuclei being severely affected by the pathological process in PSP resulting in midbrain atrophy, the dentate nucleus of the cerebellum is involved. Its main efferent pathway is the brachium conjunctivum or superior cerebellar peduncle (SCP). Its fibres pass into the brainstem and decussate at the level of the inferior colliculi before synapsing in the red nucleus and the ventrolateral nucleus of the thalamus. Signal change in this structure may be seen in PSP but is not particularly sensitive. Qualitative

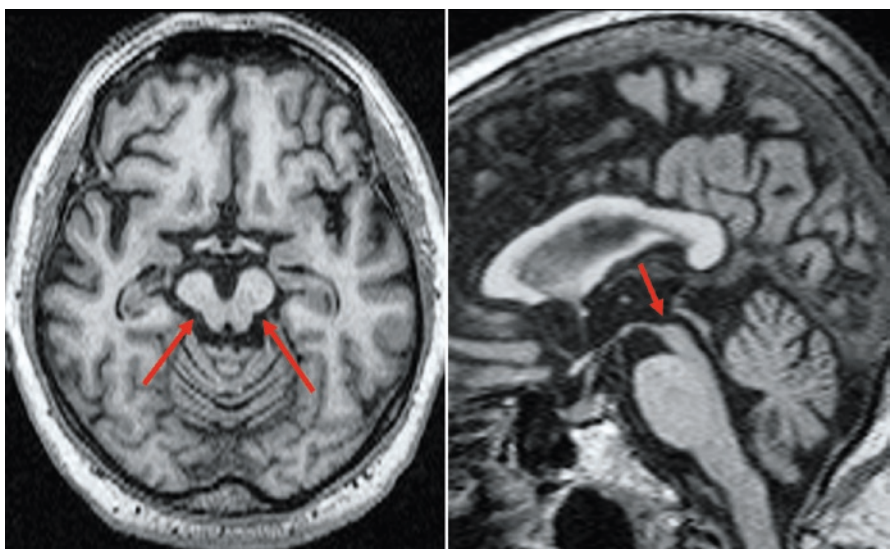


**Fig. 5.39** Mesencephalic atrophy. Axial (*left*) and sagittal (*right*) T1 MR demonstrating striking midbrain atrophy in pathologically proven PSP

**Table 5.12** MRI features in atypical Parkinsonian syndromes

| | MRI technique | Imaging feature | Discriminates |
|---|---|---|---|
| Progressive supranuclear palsy (PSP) | T1 (sag) | Midbrain atrophy (A-P diameter <14 mm) | PSP from MSA |
| | T1 (sag) | Concave upper midbrain border | PSP from IPD |
| | T1 (cor/axial) | Superior Cerebellar Peduncle atrophy | PSP from MSA, IPD |
| | T1 (sag) | Ratio of Midbrain:Pons area – 'hummingbird' | PSP from MSA |
| Multiple system atrophy (MSA) | T2/PD (axial) | 'Hot cross bun' or Pontine cross sign | MSA (cerebellar subtype) from PSP, IPD |
| | T2/PD (axial) | Putamen, low intensity | MSA from IPD |
| | T2/PD (axial) | Putaminal slit sign | MSA (parkinsonian subtype) from PSP, IPD |
| Cortico-basal degeneration (CBD) | T1 | Global atrophy | Seen in advanced PSP as well |
| | T1 | Asymmetric cortical atrophy | More suggestive of CBD than PSP or MSA |

*IPD* idiopathic Parkinson disease

judgements of SCP volume on axial and coronal T1 MRI may be more useful suggesting sensitivities and specificities of 75% and 95% and these findings are supported by separate pathological studies (Fig. 5.40).

Biological variation in normal anatomy is bound to contribute to overlap in quantitative data and requires adjustments to be made. Quantitative brainstem measurements harbour potential as diagnostic aids in degenerative Parkinsonian disorders. Especially the midbrain to pons ratio is helpful in differentiating PSP from MSA (Fig. 5.41).

In terms of linear measurements, PSP can be differentiated from MSA-P using a midbrain diameter <14 mm on the sagittal scan (A-P diameter), but between 20% and 40% of patients cannot be correctly classified either because no characteristic changes were seen, or because changes occur in both conditions.

A ratio of linear measurements accounts in part for this variability and this can be improved by employing volumetric MRI to asses the true volume of the brainstem structures. While more labour intensive, resulting measurements more reliably discriminate the degenerative causes of Parkinsonism (Fig. 5.42).

Regional ADC measurements from the middle cerebellar peduncle are capable of discriminating PSP and MSA with a sensitivity and specificity of 91% and 84% on the basis that the ADC in the tissue concerned is abnormal in MSA. Clear abnormalities in PSP have not been established. Diffusion tensor imaging and tractography demonstrates promise in this regard, but at present this remains a research tool (Fig. 5.43).

There is no specific molecular probe for SPECT/PET in PSP. FDG-PET may show hypometabolism in the frontal lobes as in FTLD, and also in the mid-brain. The specificity of these findings is uncertain, and no clear indication exists.

#### 5.4.3.5 Differential Diagnosis

PSP remains a clinical diagnosis and most investigations are conducted to exclude alternative diagnoses (Box 5.5). CSF examination and quantification of Tau protein remains a research tool and may not discriminate different degenerative diseases well, but is still offered in some specialist centres. In case of doubt, follow-up imaging can be used to demonstrate progressive atrophy (Fig. 5.44).

### *5.4.4 Multiple System Atrophy (MSA)*

*Dominic Paviour*

**Synonyms**

Shy Drager syndrome; Striatonigral degeneration (SND); Olivopontocerebellar atrophy (OPCA);

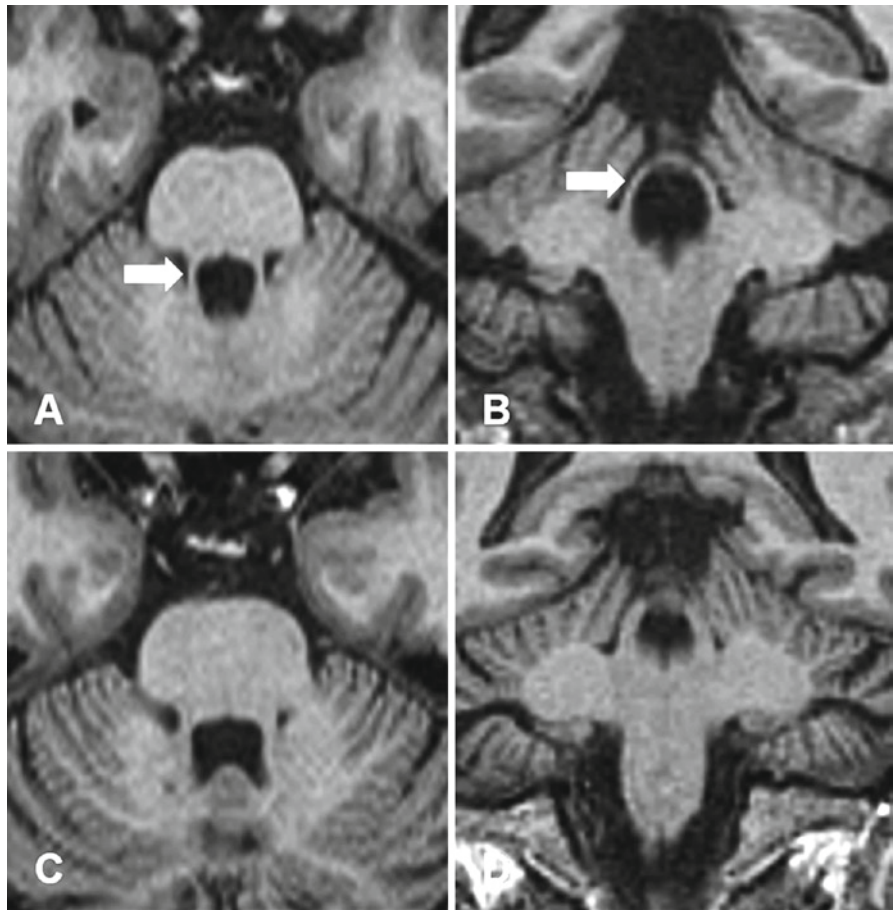



**Fig. 5.40** Atrophy of the superior cerebellar peduncle in PSP. (**a** and **b**) Axial and coronal T1 section in PSP showing a thin Superior Cerebellar Peduncle (*arrow*). (**c** and **d**) Axial and coronal T1 section in healthy control for comparison

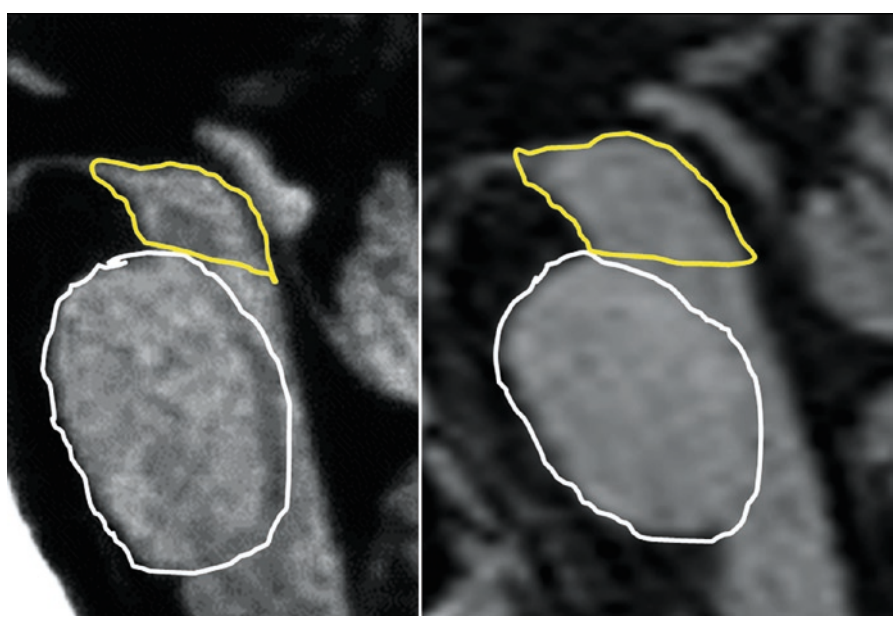


**Fig. 5.41** Sagittal T1-weighted MR illustrating area measurements of midbrain and pons in PSP (*left*) and MSA (*right*). Note also the flattening of the superior profile of the midbrain in PSP

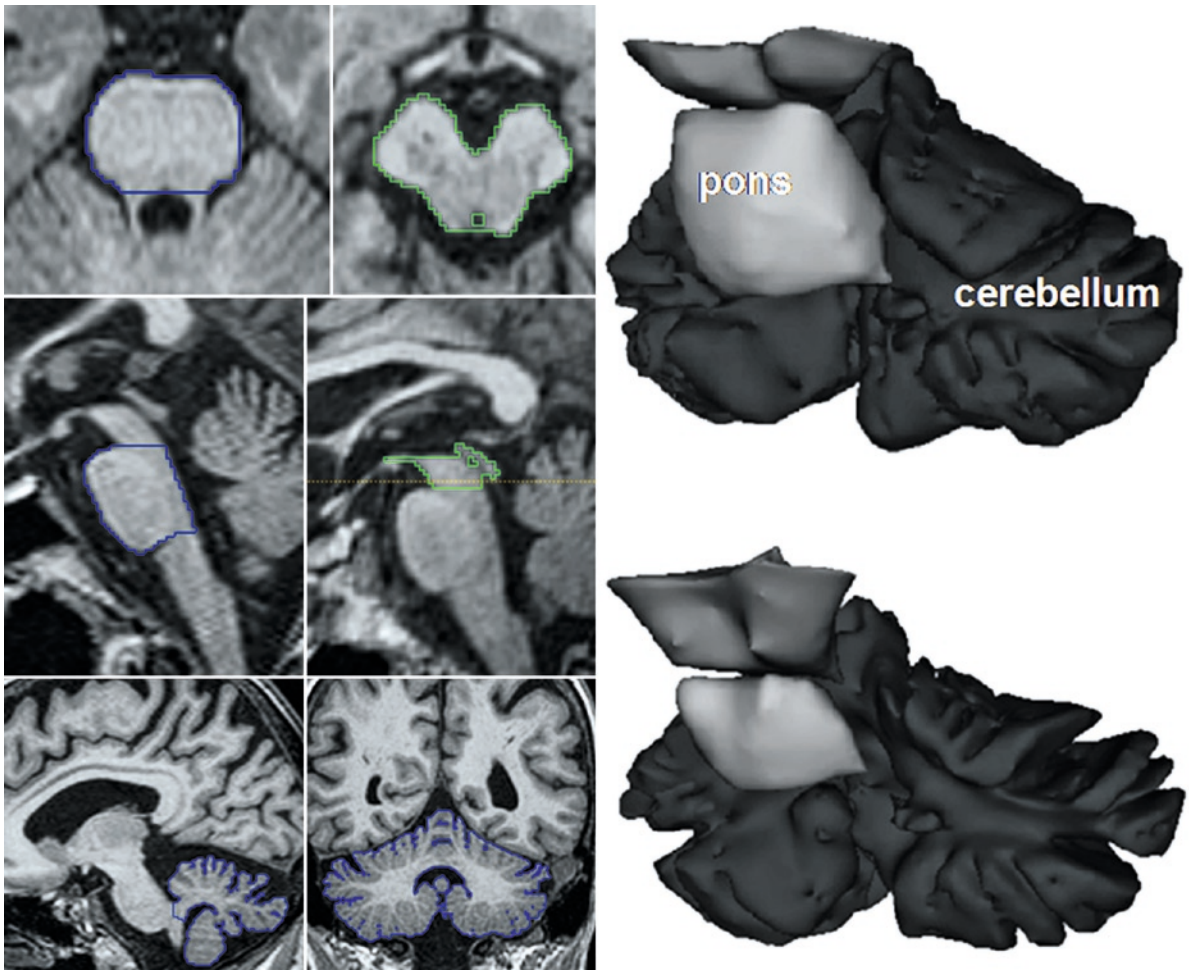



**Fig. 5.42** Regional segmentation of brainstem structures in MSA (*blue*) and PSP (*green*) with computer generated 3D volume reconstructions for illustration. Smaller midbrain volumes differentiate PSP from MSA and smaller pontine and cerebellar volumes differentiate MSA from PSP

#### 5.4.4.1 History

Olivopontocerebellar atrophy (OPCA) and striatonigral degeneration (SND), which are the predominant pathological correlates of what is now known as multiple system atrophy (MSA) were described independently in 1900 and 1961. The Shy-Drager syndrome has historically been the term used to describe the less common phenotypic presentation of MSA with predominant autonomic failure. Graham and Oppenheimer first proposed the term MSA based on the finding that sporadic OPCA, SND and Shy–Drager syndrome co-exist both clinically and pathologically.

#### 5.4.4.2 Clinical Presentation

Multiple system atrophy (MSA) is a sporadic adult-onset neurodegenerative disease, which usually presents clinically as a combination of parkinsonism, cerebellar ataxia and autonomic failure. Which of these phenotypes is foremost depends on whether the patient is deemed to have MSA-P, the predominantly parkinsonian phenotype which is the commonest, MSA-C (cerebellar) or MSA-A, (autonomic failure), the last of these being least common. It is a disease of later adult life, with a mean age at onset of 58 years (with a range from mid 30s to 80s). Dementia was historically not thought

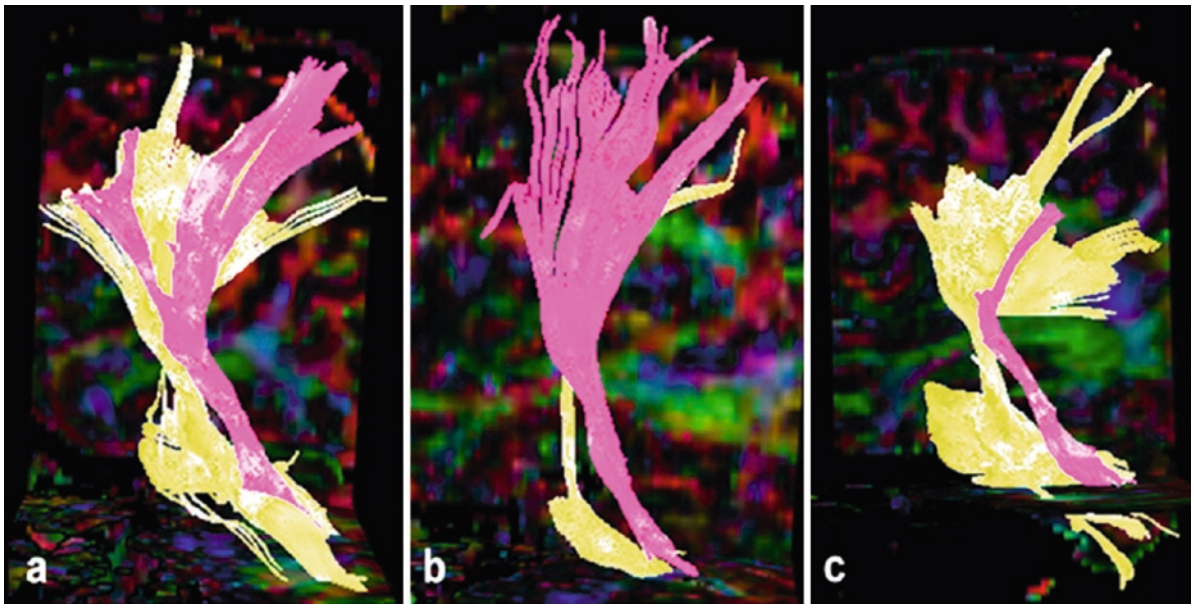



**Fig. 5.43** DTI analysis in PSP versus MSA. Tractography of the middle cerebellar peduncle (MCP in *yellow*) and superior cerebellar peduncle (SCP in *purple*) in idiopathic Parkinson disease (**a**), MSA (**b**) and PSP (**c**). Note selective atrophy of the MCP in the patient with MSA and of the SCP in the patient with PSP. (Reprinted with permission from Nilsson Neuroradiology 2007;49:111–9)

## Box 5.5 Differential diagnosis of PSP

*Degenerative*
CBD (alien limb syndrome, cortical sensory deficits, limb apraxia, dystonia, asymmetric bradykinesia)
Parkinson's disease (tremor-dominant disease, levodopa response, less axial rigidity)
Dementia with Lewy bodies (hallucinations, cortical dementia, fluctuations, parkinsonism)
MSA (prominent cerebellar symptoms, autonomic dysfunction, parkinsonism)
CJD (duration <1 year with dementia, myoclonus, abnormal findings on EEG)
HD (family history, findings on genetic test)
Spinocerebellar ataxia (SCA) (family history, cerebellar signs, findings on genetic test)
FTLD-MND/FTLD-U (lower motor neuron signs, abnormal electromyograph [EMG] findings)

*Other*
Cerebrovascular disease (focal features, imaging findings)
Whipple's disease (ocular-masticatory myorhythmia, polymerase chain reaction [PCR] confirmation)
Neurosyphilis
Normal pressure hydrocephalus (dementia, urinary dysfunction, gait abnormality, imaging findings)
Wilson's disease (Kayser–Fleischer rings, earlier onset, copper metabolic abnormalities)
Iatrogenic secondary to Neuroleptic medication

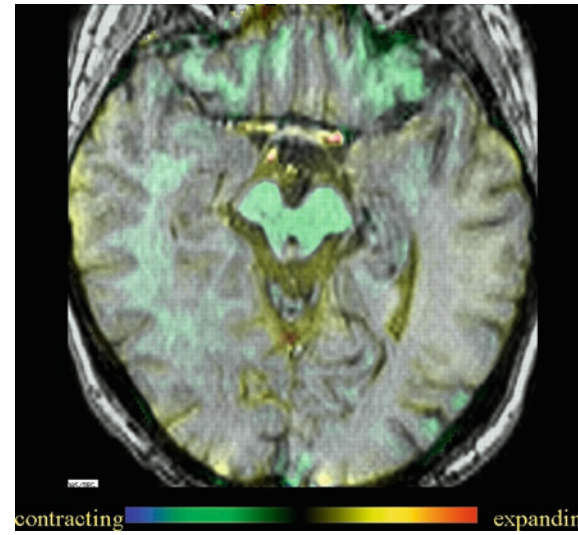



**Fig. 5.44** Sequential MRI scans in a case of PSP (1 year interval) registered using Fluid registration. Note high rates of atrophy in the midbrain (*green*) and some inferior frontal degeneration and ventricular expansion (*yellow*)

**Table 5.13** Clinical signs and symptoms suggestive of MSA rather than idiopathic Parkinson's disease

| |
|---|
| Jerky postural component to the tremor |
| Myoclonic jerks |
| Rapid disease progression with early instability and falls are common to MSA (and PSP) |
| Cold, dusky, violaceous extremities |
| Rapid eye movement (REM) sleep behaviour disorder |
| Sleep apnoea |
| Quivery croaky strained element to speech |
| Facial dystonia |
| Head drop/antecollis |
| Early autonomic failure |
| Cerebellar ataxia |
| Early uro-neurological dysfunction |
| Early erectile impotence in men |
| A lack of sustained levodopa responsiveness. |

to be part of MSA – however cognitive decline (usually frontal) can occur and may be severe. The parkinsonian phenotype may be very difficult to distinguish from idiopathic Parkinson's disease, presenting with a typical asymmetric tremor. Red flags suggesting MSA rather than PD are listed in Table 5.13.

In MSA-P particularly, there may be antecollis (marked forward flexion of the neck due to dystonia of the anterior neck muscles). Laryngeal dystonia may result in marked inspiratory stridor and compromise, necessitating tracheostomy. The disease is progressive, with a mean duration to death of 7 years (range 2–16). There is no (curative) treatment for MSA beyond anti-parkinsonian medication.

#### 5.4.4.3 Histopathology and Genetics

The pathological basis of MSA is oligodendroglial cytoplasmic inclusions. These stain heavily for α-synuclein, a protein which when dysfunctional has a pivotal role in the development of MSA. Macroscopically, there is predominant brainstem and cerebellar atrophy; however, marked cerebral atrophy has been reported.

In MSA-C, which is characterized clinically by predominant cerebellar ataxia, the pathological findings are primarily those of neuronal cell loss and gliosis in the inferior olivary nucleus, pontine nuclei, cerebellar hemispheres and vermis, whereas in MSA-P, neuronal cell loss and gliosis is most severe in the substantia nigra, putamen, caudate nucleus and globus pallidus. Neurodegeneration in the autonomic nervous system (the Shy–Drager syndrome) presents clinically with prominent autonomic failure. It was not until the subsequent discovery of the oligodendroglial cytoplasmic inclusions that the notion of MSA as a single clinico-pathological entity could be confirmed.

A spectrum of pathological phenotypes of MSA exists and is the basis for the variation in the clinical phenotype. Less severe pathological involvement of the nigro-striatal system is required for parkinsonism than involvement of the cerebellum for ataxia. This may explain why the MSA-P phenotype is predominant.

Given the molecular pathology of the cellular inclusions, the α-synuclein gene is the most probable gene responsible for MSA pathogenesis. However, genetic analysis of pathologically confirmed MSA cases has failed to find any pathogenic mutations in the α-synuclein gene.

#### 5.4.4.4 Neuroimaging Findings

As with PSP, the clinical application of MRI in MSA is in discriminating it from the other degenerative parkinsonian disorders (see Table 5.12). In MSA, and particularly the cerebellar subtype, abnormalities on T1-weighted MRI are confined to the posterior fossa with predominant pontine and cerebellar atrophy.

The so-called *hot cross bun* sign on T2-weighted MRI has been proposed as a useful clinical marker of MSA-C (Fig. 5.45). This MR finding is best appreciated on proton-density weighted or FLAIR images. While initially felt to be pathognomic of MSA-C, it may in fact occur in the advanced stage of other diseases including CNS vasculitis, paraneoplastic syndromes and the spinocerebellar ataxias (SCA).

Signal change in the basal ganglia on T2 MRI is considered a more characteristic finding with low signal evident in the putamen and a thin rim of hyperintensity noted at the lateral posterior putaminal rim, particularly in MSA-P.

As well as these qualitative findings, quantitative MRI studies have confirmed the presence of regional volume loss in MSA as well as increased rates of regional atrophy conforming to the severity of regional pathology, although these rates of atrophy do not allow discrimination of MSA from other degenerative forms

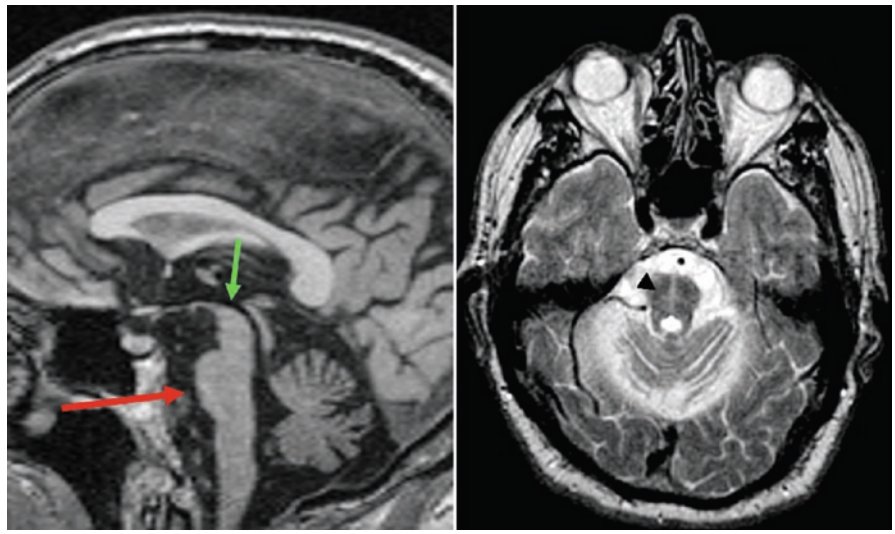


**Fig. 5.45** Imaging features of MSA. Mid-sagittal images (*left*) shows flattening of the pons and loss of volume (*red arrow*), transverse T2-weighted image (*right*) a 'hot-cross bun' sign (*arrowhead*). Note the normal appearance of the mesencephalon (*green arrow*), in contrast to PSP

of parkinsonism with 100% sensitivity or specificity. Brainstem volumetry demonstrates that the pons and cerebellum are more severely affected in MSA than in PSP.

Diffusion-weighted imaging allows MSA to be differentiated from PD on the basis of higher regional apparent diffusion coefficients (ADC) measured in the putamen, with a high sensitivity and specificity. However, as already stated, in order to apply this clinically, normal control values need to be measured for a specific scanner.

## 5.4.5 Cortico-Basal Degeneration (CBD) and Other FTLD Tauopathies

*Dominic Paviour*

**Synonyms**

Cortico-basal ganglionic degeneration

### 5.4.5.1 History

The syndrome of CBD was first recognised formally by Rebeiz in 1967, and at the time was named 'Cortico-dentato-nigral degeneration with neuronal achromasia' on the basis of the pathological findings associated with the clinical features of the disease. It was officially recognised as a specific neuropathological disease entity in 1996; however, the clinical 'Cortico-basal syndrome' can arise as a result of numerous differing underlying pathological processes.

CBD is a tauopathy with hyper-phosphorylation of microtubule associated tau protein (MAPT), like PSP, FTLD. These conditions may have significant overlap in their clinical phenotypes but are regarded as separate clinico-pathological entities albeit with a similar pathological basis.

### 5.4.5.2 Clinical Presentation

CBD typically presents in the sixth to eighth decades (mean 63 years), and is relatively uncommon although its true incidence and prevalence are unknown. Most of the published literature on CBD comes from movement disorder clinics and thus the documented clinical features at presentation are biased towards the motor manifestations of the disease. However, CBD is possibly as likely to present as a cognitive syndrome, but as these patients present to dementia clinics, this aspect of the clinical syndrome is likely to be under-reported.

The typical clinical features of the cortico-basal syndrome are presentation with a rigid, dystonic, akinetic or dyspraxic arm. Occasionally, patients may describe a striking phenomenon where a limb 'has a will of its own' and it may be observed that the arm may 'wander' and rarely may grasp hold of other body parts, people close by or bedclothes. This is the 'alien limb' phenomenon and it is typically associated with

| Differential diagnosis of MSA |
|---|
| *Degenerative* |
| Parkinson's disease (tremor-dominant disease, levodopa response) |
| Dementia with Lewy bodies(hallucinations, cortical dementia with aphasia, parkinsonism) |
| PSP (earlier falls, no cerebellar signs, sub-cortical dementia with apathy) |
| Spinocerebellar ataxia (SCA) (family history, cerebellar signs, findings on genetic test) |
| Other AD/AR cerebellar ataxias |
| Idiopathic Orthostatic Hypotension and other Autonomic Failure Syndromes |
| *Other* |
| Multiple Sclerosis (typical imaging findings, spasticity, ataxia, minimal extra-pyramidal features) |
| Cerebrovascular disease (focal features, imaging findings) |
| Whipple's disease (ocular-masticatory myorhythmia, polymerase chain reaction [PCR] confirmation) |
| Neurosyphilis |
| Wilson's disease (Kayser–Fleischer rings, earlier onset, copper metabolic abnormalities) |
| Iatrogenic secondary to Neuroleptic medication |

cortical sensory loss. Patients may also initially complain of a gait disorder. Other presentations with behavioural disturbance, speech and language dysfunction and sensory symptoms are less common. Ultimately, most develop asymmetric parkinsonism (particularly bradykinesia and rigidity) and marked dyspraxia of affected limbs as well as gait impairment.

Many patients have a tremor, but this is different from that seen in Parkinson's disease, in that it is faster, more irregular and jerky and particularly in the later stages of the disease has a stimulus-sensitive myoclonic component. Apraxia may be bilateral but may be more easily elicited in the less parkinsonian upper limb. Gait apraxia may result in an abnormal gait, with the foot sticking to the floor or being dragged along.

Cognitive dysfunction in CBD is common and this is reflected in the revised diagnostic criteria. Aphasia may be seen in as many as 44% of patients. Frontal executive impairment is common and consistent with the known pathological involvement of the parietal lobe calculation and visuo-spatial skills are also commonly impaired. Cognitive impairment may remain the dominant feature of the disease, making clinical diagnosis difficult.

Clinical diagnosis of CBD is less reliable than the other parkinsonian disorders (a sensitivity of around 50% in the late stages of the disease, compared to 80–90% for a clinical diagnosis of PSP when the diagnostic criteria are fulfilled). The clinical diagnosis in life is difficult and when the disease presents as a movement disorder, PSP is the disorder it is most commonly confused with. The commonest cognitive presentations may be difficult to distinguish clinically from the progressive non-fluent aphasia and the FTD subtypes of FTLD. AD (dyspraxic presentations) is a common cause of misdiagnosis of CBD. There is no treatment for CBD.

#### 5.4.5.3 Histopathology and Genetics

A definitive diagnosis of CBD as the basis for the cortico-basal syndrome can only be made at post-mortem. Macroscopically, atrophy is centred on the posterior frontal and parietal cortex with relative sparing of the temporal and occipital regions (Fig. 5.20). Cortical atrophy is classically asymmetric; however, whether this is the case in the more cognitive and less 'asymmetric motor' presentations of the disease is not established.

Normal cortical architecture is destroyed and there is cell loss and gliosis. Similar pathology occurs in the substantia nigra with loss of pigmented cells. The 'neuronal achromasia' originally described is characteristic of the pathology. Affected cortical neurons stain positively for tau and ubiquitin. The distribution and number of 'ballooned neurons' is crucial for the differential diagnosis. The molecular basis of CBD, as in PSP is the accumulation of hyper-phosphorylated tau forming abnormal filamentous inclusions in neurons and glia. As is the case in PSP, CBD is a four repeat tauopathy (see also Sect. 5.3).

No confirmed genetic basis for CBD has been established; however, rare reports of pathologically confirmed familial CBD have been published.

#### 5.4.5.4 Neuroimaging Findings

There have been very few MRI studies of CBD in which pathological confirmation of the diagnosis has been available. This means that in a clinical syndrome with a potentially diverse pathological basis, the documented MRI findings are not likely to be reliable indicators of the underlying neuropathology. Nevertheless, it is likely that in the early stages of the disease, the imaging findings will be normal. As the disease progresses, the macroscopic asymmetric cortical atrophy that is evident at post-mortem may be apparent on volumetric T1-weighted MRI. Asymmetric parasagittal atrophy may be a feature of CBD (Fig. 5.46). Midbrain atrophy and ventricular dilatation are supportive of the clinical diagnosis of PSP and asymmetric cortical atrophy supports the clinical diagnosis of CBD, but no MRI finding is truly specific for CBD. In fact, asymmetric AD is a much more common pathology than CBD and should always be considered in the differential diagnosis.

Functional imaging studies (perfusion/metabolism on SPECT/PET) may show the asymmetric loss of function which might be predicted in any patient with the cortico-basal syndrome – its diagnostic reliability is unclear.

## 5.5 Dementia in 'Other' Movement Disorders

### *5.5.1 Introduction*

The previous chapter discussed disorders where the clinical phenotype is predominantly dementia accompanied by parkinsonism. This chapter focuses on

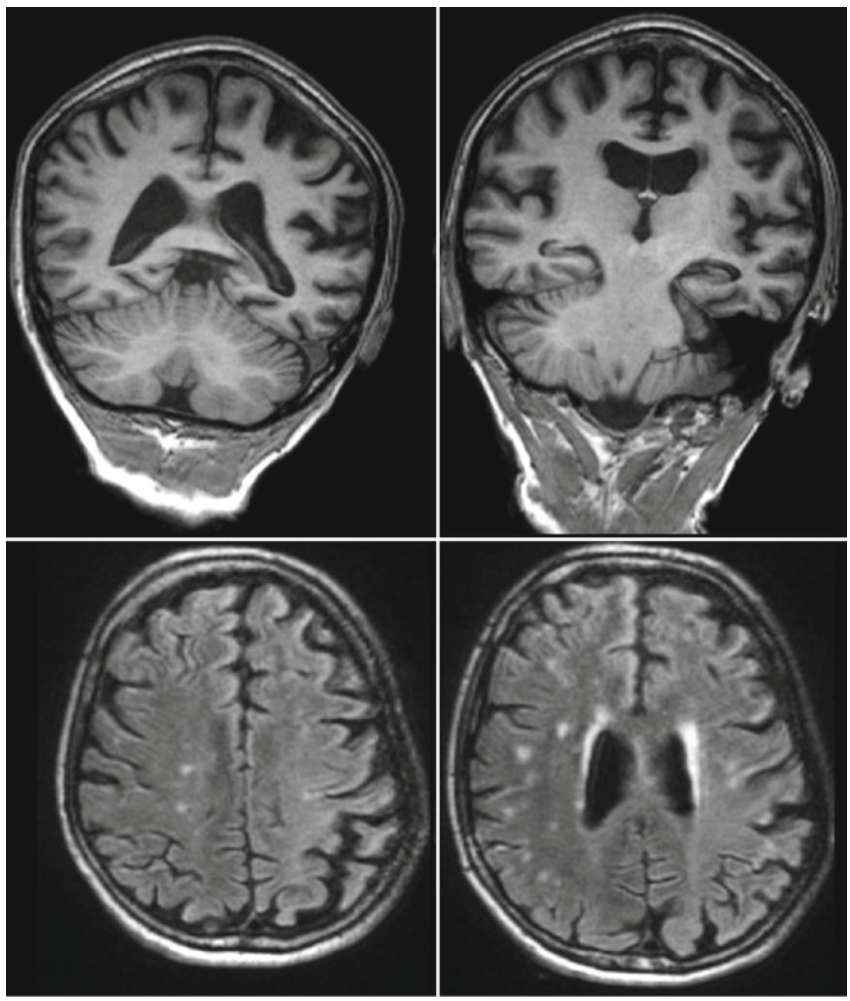


**Fig. 5.46** Asymmetric cortical atrophy in CBD. This 67-year-old woman presented with speech difficulties, memory complaints and apraxia. She had difficulties operating household tools and lost control over her right hand. Coronal T1-weighted (*top*) and axial FLAIR (*bottom*) MRI showed markedly asymmetric left hemispheric atrophy, mostly affecting the parietal and temporal lobe

cognitive decline accompanied by non-parkinsonian movement disorders – with or without additional parkinsonism; these groupings do not have clear boundaries and there is inevitably overlap. Nonetheless, the broad clinical and imaging phenotype is key to differential diagnosis and to the imaging strategy and has determined the organisation of this book. Our approach may mean that conditions with common aetiologies but different phenotypes may be dealt with in separate chapters. For example, the trinucleotide repeat disorders of Huntington's disease (HD) and dentatorubral-pallidoluysian atrophy (DRPLA) are covered in this chapter, but another repeat disorder – fragile-X pre-mutation – is covered in Chap. 7, since the key MR feature is white matter hyperintensity; furthermore, the spino-cerbellar ataxias (SCAs) will not be considered at all because cognitive decline is a less prominent or only a late feature. Normal pressure hydrocephalus produces cognitive decline with a movement disorder – characteristically a subcortical cognitive profile and an abnormal gait – and this will be discussed in Chap. 8. As with many chapters, the diverse nature of cerebrovascular disease means it needs to be considered in the differential for a range of presentations – in particular, vascular dementia may be associated by a wide range of neurological features including an abnormal gait, motor signs or a movement disorder depending on the sites of lesions.

Table 5.14 presents a summary (but not comprehensive) list of disorders where dementia and a movement disorder may be part of the presentation or appear sequentially – and shows how multi-system presentation spans a range of aetiologies and phenotypes (and hence chapters).

## 5.5.2 Huntington's Disease

*Ed Wild, Nicola Hobbs, and Susie Henley*

**Synonyms**

Hereditary chorea; Huntington's chorea; Chorea major

### 5.5.2.1 History

The first description of Huntington's disease (HD) was by George Huntington in 1872. He noted that 'as the disease progresses, the mind becomes more or less impaired, in many amounting to insanity, while in others mind and body both gradually fail until death relieves them of their sufferings'. Huntington's disease usually causes a frontal/subcortical dementia.

**Table 5.14** Dementia and movement disorders: an overview

| Disorder | Type of movement abnormality | Chapter |
|---|---|---|
| Lewy body disease (DLB) and Parkinson's disease dementia | Parkinsonian | 5.4 |
| Multiple system atrophy (MSA) | Cerebellar and extrapyramidal | 5.4 |
| Progressive supranuclear palsy (PSP) | Falls, parkinsonism, axial rigidity | 5.4 |
| Amyotrophic lateral sclerosis (ALS) & FTD-MND | Upper motor neuron & lower motor neuron deficits | 5.3 |
| Corticobasal degeneration (CBD) | Dyspraxia, dystonia, myoclonus and parkinsonism | 5.4 & 5.3 |
| Huntington's disease (HD) and DRPLA | Chorea, bradykinesia, ataxia | 5.5 |
| Neurodegeneration with brain iron accumulation (NBIA) | Parkinsonism, dystonia | 5.5 |
| Creutzfeldt–Jakob disease (CJD) | Myoclonus, ataxia | 5.6 |
| Alcohol/Drugs | Ataxia, variety of pyramidal/extrapyramidal | 5.7 |
| Vascular dementia (VaD) – large vessel | Focal upper motor neuron signs | 6.3 |
| Small vessel VaD | Gait abnormalities, lower-body parkinsonism | 6.4 |
| Leukodystrophies | Pyramidal and extrapyramidal, ataxia | 7 |
| Multiple sclerosis (MS) | Wide range – including ataxia, focal UMN signs | 7 |
| Normal-pressure hydrocephalus (NPH) | Slow and unsteady apraxic gait | 8 |

#### 5.5.2.2 Clinical Presentation

The clinical presentation of HD is usually in early adulthood or middle age and characterized by a progressive triad of chorea, psychiatric (behavioural) disturbances and cognitive deterioration. Chorea is the most conspicuous manifestation, but decline of cognitive function becomes evident in nearly all patients and often precedes the onset of motor manifestations. The cognitive dysfunction consists of slowing of mental processes, impaired attention and executive functions, loss of concentration, loss of problem-solving, and ultimately dementia. Psychiatric features of HD include apathy, irritability, depression, anxiety and sometimes compulsive behaviour or aggression. A family history is usually clear but may be obscured: non-paternity or loss of contact with parents or because of censuring and/or anticipation – age at onset becoming earlier in subsequent generations.

There is no cure for Huntington's disease, but relief of symptoms is often possible. Chorea is seldom distressing to the patient but is frequently amenable to treatment with neuroleptics or tetrabenazine. Psychiatric manifestations often respond well to conventional drug therapy. Disease-modifying therapies are being actively sought but none are yet proven.

#### 5.5.2.3 Genetics, Pathogenesis and Histopathology

Huntington's disease is inherited in an autosomal dominant manner, with nearly 100% penetrance and a low spontaneous mutation rate. The causative gene (*HTT*, also known as *IT15* – 'Interesting Transcript') is located on chromosome 4 and contains an excessive number of trinucleotide CAG repeats, encoding a polyglutamine stretch within the protein huntingtin. The protein is widely expressed in both neuronal and non-neuronal tissues. It has also been found in neurofibrillary tangles and neuritic plaques in AD and in Pick bodies, suggesting a neuropathological connection between these neurodegenerative disorders. The normal number of CAG repeats is 8–39, usually less than 35. In patients with Huntington's disease, the number of repeats varies from 40 to over 100. Subjects with over 60 repeats are likely to develop juvenile HD. As with other trinucleotide syndromes, the number of repeats can increase over generations leading to an earlier age at onset and increased severity – a phenomenon called anticipation.

In terms of pathogenesis, mutant huntingtin is thought to lead to a toxic gain of function through which multiple cellular changes produce the HD pathology. Neuronal damage first appears in the striatum and loss in the striatum occurs in a systematic fashion. The progression is from medial to lateral in the caudate nucleus and in a dorso-ventral direction in the putamen. The projection fibres from the striatum are the most severely affected in Huntington's disease. The medium-sized spiny GABA-ergic projection neurons are particularly vulnerable. Microglial activation is seen before the onset of clinical signs and may contribute to the pathogenic process. The loss of central connection pathways, in particular in the fronto-thalamic area, may well explain the progressive subcortical dementia and the psychiatric disorders.

On macroscopic inspection, the brain may show cortical atrophy, ranging from mild to severe. Atrophy is seen throughout the cortex, but most conspicuous in the caudate nucleus, the putamen and the globus pallidus. The atrophy of the caudate nucleus is most striking on coronal slices (Fig. 5.47). Histologically, the atrophy is associated with loss of neurons and astrocytosis. The severity of atrophy of the caudate nucleus corresponds with both the number of CAG repeats and the clinical severity and progression of disease. Neuronal loss is also found in the hippocampus, hypothalamus and pars reticularis of the substantia nigra.

#### 5.5.2.4 Differential Diagnosis

Clinically, HD closely resembles a number of rare syndromes referred to as Huntington's disease phenocopies or Huntington's disease-like (HDL) syndromes, but the diagnosis of HD in symptomatic patients can be made with certainty on the basis of genetic testing. In neuroacanthocytosis, there is comparable atrophy of the caudate nucleus and putamen as well as abnormal red cell morphology, neuropathy, myopathy, epilepsy, elevated creatine phosphokinase and orofacial dystonia. HDL1 (a familial prion disease), HDL2 (caused by *JPH3* mutations), HDL4 (spinocerebellar ataxia

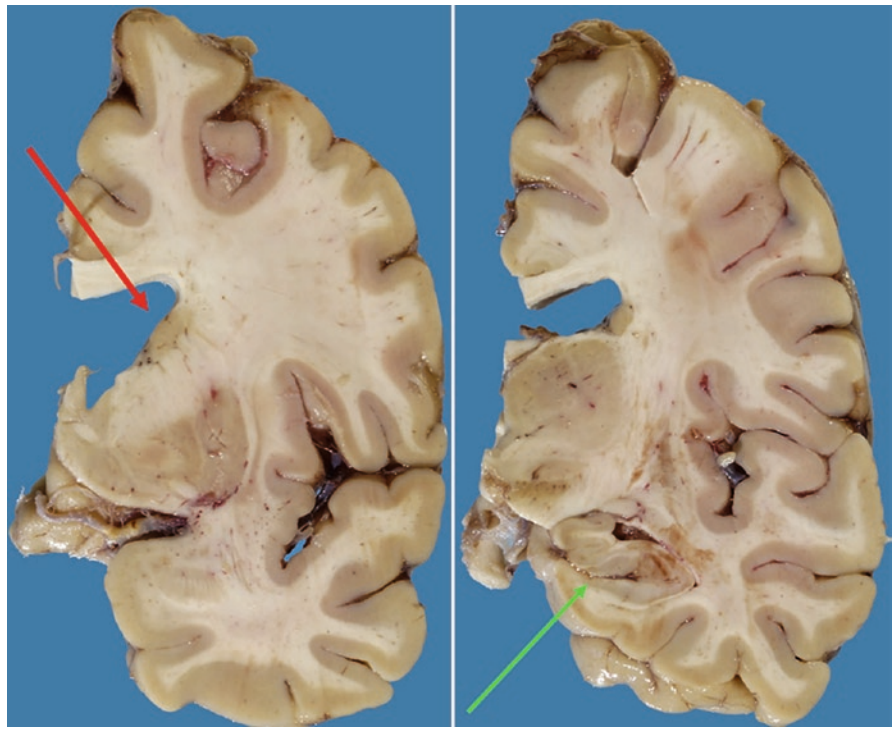


**Fig. 5.47** Gross macroscopy of Huntington's disease. Note ventricular widening due to atrophy of the caudate nucleus, which appear flattened (*red arrow*). As a consequence, the frontal horn of the lateral ventricle has enlarged, while the temporal horn is normal, since there is no hippocampal atrophy (*green arrow*)

type 17) and neuroferritinopathy all resemble HD and can be diagnosed genetically. The brain iron accumulation disorders NBIA1 and NBIA2, which may mimic HD clinically, invariably produce reduced signal in the basal ganglia on T2*-weighted MRI (Sect. 5.5.3). There are many other diseases that may present with chorea, such as Sydenham's chorea, and any conditions – be they infectious, inflammatory, toxic or vascular – that involve the striatum.

#### 5.5.2.5 Neuroimaging Findings

MRI reveals a variable degree of cortical thinning and atrophy of the striatum, most conspicuous on visual inspection in the caudate nucleus which is best viewed coronally. Striatal atrophy is present prior to clinical manifestation of motor signs and caudate volume has been shown to be a good predictor of motor onset. Striatal atrophy rates may be increased up to 10 years prior to motor onset. Cortical atrophy is present in the pre-motor onset population but becomes more notable and can be fairly widespread in later stages by which time the caudate can be reduced to a thin rim around the ventricle (Fig. 5.48). In addition, grey matter reductions can be seen in the hypothalamus and opercular cortex.

There is a correlation between the degree of cortical and caudate atrophy and dementia and chorea, respectively. The reduction in volume of the putamen and degree of reduction of dopamine ligand binding are correlated with the degree of cognitive deficits. White matter volume is also reduced and is associated with decreased cortical and striatal glucose uptake and frontal-executive task performance (Fig. 5.49).

Selective atrophy of the caudate nucleus and putamen can also be seen in post-hypoxic ischemic encephalopathy, after bilateral infarctions of the caudate nucleus, in Sydenham's chorea (often unilateral) and in infectious-inflammatory disorders, neurometabolic disorders and toxic encephalopathies. In some of these cases the encephalopathy is static, or the history and other clinical findings will lead to the proper diagnosis. Many other neurodegenerative disorders can be accompanied by atrophy of the caudate. Caudate atrophy has also been described in AD, CJD, HIV-dementia, DRPLA, SLE, MS and selectively in neuroacanthocytosis.

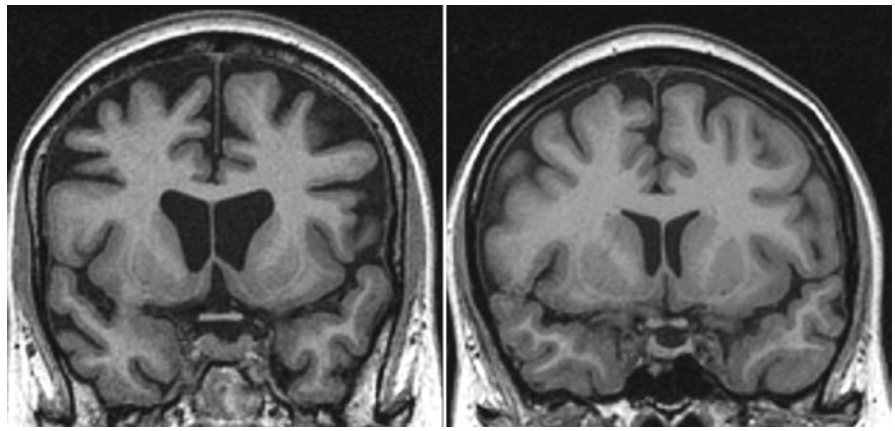


**Fig. 5.48** Coronal MRI in HD. Compare the T1-weighted images of a 43-year-old patient with HD on the *left* (duration 8 years) with the 43-year-old gender-matched control on the *right*. Note enlarged ventricles due to volume loss of the putamen and caudate. The latter appear shrunken and the caudate-ventricle border is much less convex in the HD patient. Cortical thinning and sulcal widening is also apparent

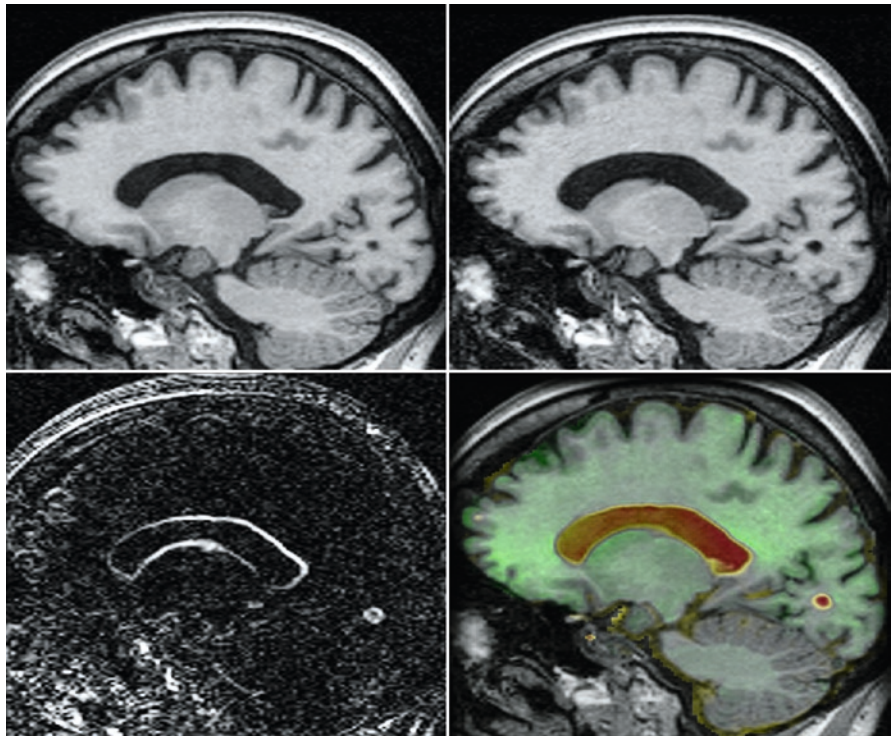


**Fig. 5.49** Longitudinal MRI in HD. T1-weighted sagittal images of the patient from Fig. 5.48 showing *top left* baseline, *top right* follow-up 27 months later, *bottom left* difference image and *bottom right* fluid-registered image. Caudate loss, ventricular expansion and sulcal expansion is evident, and confirmed by the difference image; the fluid image illustrates that by this stage in the disease ongoing loss (in *green*) is extensive beyond the caudate – note the frontal white and grey matter atrophy

PET shows promise in the functional analysis of the basal ganglia and has demonstrated striking changes in metabolic rate (FDG), dopamine receptor density and microglial activation in premanifest and early HD (Fig. 5.50). It has also been used to assess striatal graft treatment. fMRI has shown reduced BOLD responses in premanifest gene carriers relative to controls, sometimes in the absence of measurable clinical or cognitive deficits. MR spectroscopy has been inconclusive and is unlikely to be as sensitive as other imaging modalities in HD.

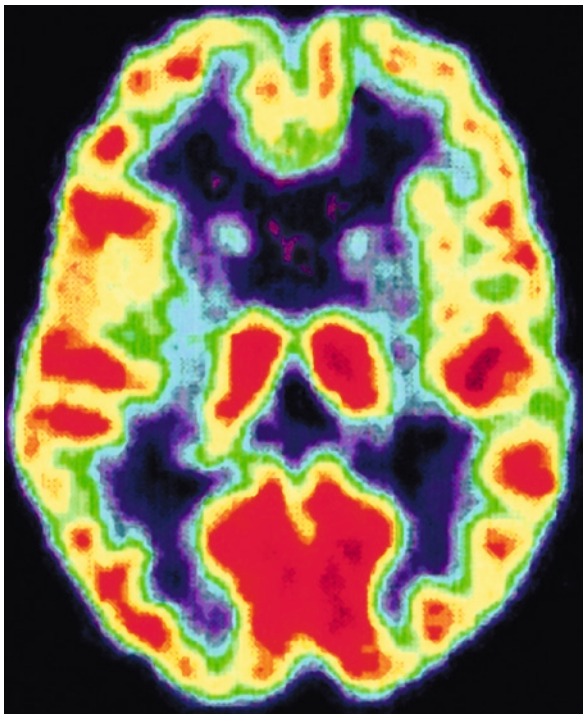


**Fig. 5.50** [18F]Fluoro-deoxyglucose PET image in HD. Complete lack of uptake in the caudate nuclei which appear blue rather than red. Notice the preserved metabolism in the thalamus. (Courtesy of Gary Small, M.D., UCLA, USA)

## *5.5.3 Metal Metabolism Disorders*

**Synonym**

Familial hepato-lenticular degeneration

### 5.5.3.1 Introduction

Several disorders in the metabolism of metals lead to neuropsychiatric, cognitive and other neurological problems due to metal accumulation in specific brain structures. Those primary disorders of metal metabolisms will be discussed in the current chapter. Other metal metabolism disorders, such as Menkes' disease will not be considered, since dementia is not a lead symptom. Secondary accumulation of metals, especially iron, may occur without obvious clinical correlate in normal ageing (see Chap. 4) and also in many neurodegenerative diseases, for example in AD and Parkinson's disease and is discussed in the relevant chapters.

### 5.5.3.2 Wilson's Disease

This autosomal-recessive genetic disorder is caused by abnormal accumulation of copper in various organs, including the brain. In Wilson's disease, mutations in the ATP7B gene lead to defects in a cation-transporting P-type ATPase which results in an inability of the liver to excrete copper to the bile and in cerulopasmin. Patients may present in childhood through liver failure or in adulthood with neuropsychiatric symptoms. Excess copper accumulates in the cornea (Kayser–Fleischer rings) and in the basal ganglia of the brain. Neuropsychiatric symptoms include parkinsonism, ataxia, tremor, polyneuropathy, emotional lability, depression and personality changes, and dementia. Treatment is with chelating agents or liver transplantation (for liver failure).

#### Neuroimaging Findings

MRI tends to be abnormal in all symptomatic individuals with Wilson's disease although the specific involvement can be diverse. High signal lesions are seen on T2-weighted imaging and these are often widespread and particularly involving basal ganglia and white matter; these changes are accompanied by diffuse cerebral, midbrain and cerebellar atrophy (Fig. 5.51). The striatum shows the greatest involvement with putamen caudate and thalamus most frequently involved (and usually bilaterally) – these changes and atrophy increase with neurological severity (rather than disease duration). The classical appearance of the so-called face of the giant panda on T2-weighted axial images at the level of the substantia nigra is due to areas of hypointensity due to iron accumulation (esp. the red nucleus) and areas of high signal in the surrounding tegmentum due to gliosis and demyelination. White matter lesions occur frequently in the frontal lobes, pons or cerebellar peduncles and white matter. In some patients, high signal can be found on T1-weighted images, as in other causes of hepatocerebral

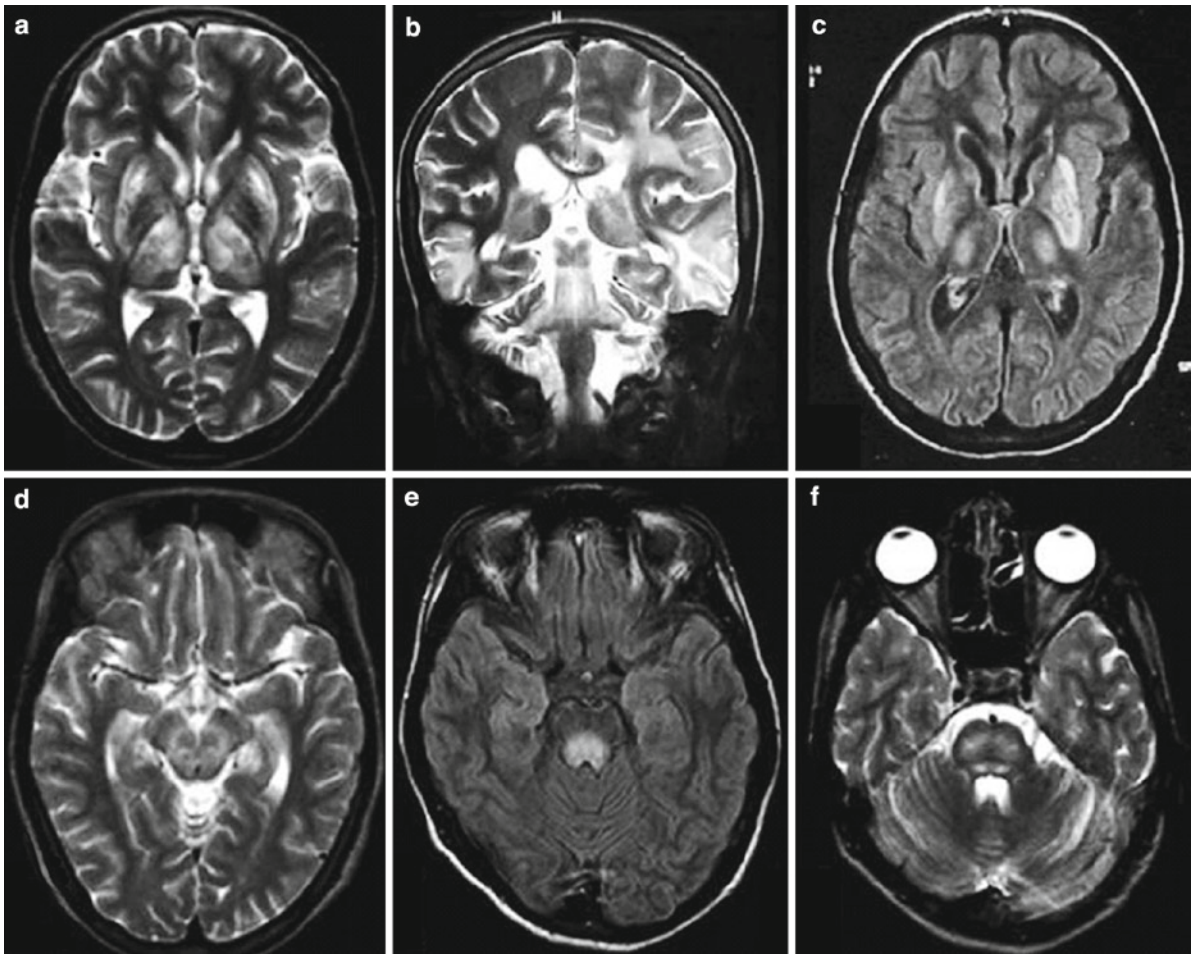



**Fig. 5.51** Brain MRI findings in patients with Wilson's disease. (**a**) T2 hyperintensity in bilateral putamen and thalamus; (**b**) Coronal T2 showing signal changes involving white matter, basal ganglia, and brain stem structures; (**c**) FLAIR image revealing signal changes in bilateral caudate, putamen, and thalamus; (**d**) Axial T2 at the midbrain level showing the 'Face of Giant Panda' sign; (**e**) FLAIR through midbrain revealing hyperintense signal changes in the tectum; F: Axial T2 through pons showing high signal similar to central pontine myelinolysis. (Reprinted with permission from Mov Disord. 2010;25:672–8)

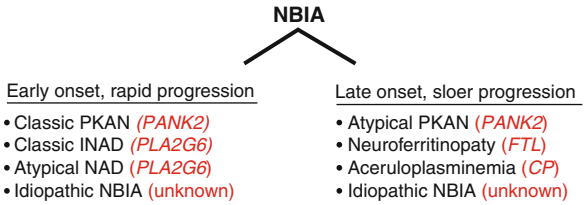
syndromes, perhaps caused by manganese deposition. SPECT/PET may show non-specific decrease of perfusion/metabolism in the basal ganglia.

### Differential Diagnosis and Work-up

Beyond genetic testing, Wilson's disease can be diagnosed based on a combination of extrapyramidal symptoms, Kayser–Fleischer rings, low ceruloplasmin level, and high urinary copper excretion (with low plasma levels).

#### 5.5.3.3 Neurodegeneration with Brain Iron Accumulation (NBIA)

NBIA refers to a group of disorders that have in common abnormal iron deposition of the brain. This descriptive term has replaced the former eponymous 'Hallervorden-Spatz syndrome'. NBIA encompasses infantile neuro-axonal degeneration which we will not consider, but also diseases that can present in adulthood with cognitive decline and dementia, notably atypical PKAN, idiopathic NBIA and aceruloplasminemia – the latter will be discussed in a bit more detail in this chapter.




Source: http://www.nbiadisorders.org/

Pantothenate kinase-associated neurodegeneration (PKAN) is caused by a mutation in the *PANK2* gene, a regulatory enzyme in the biosynthesis of coenzyme A. The mode of inheritance is autosomal recessive, but many cases present de novo mutations, either in the PANK2 gene or other unknown ones – in which case patients are referred to as idiopathic NBIA. Clinical presentation of the late-onset of the disease, 'atypical PKAN', is in the second or third decade with extrapyramidal symptoms (dystonia and rigidity), speech abnormalities, and psychiatric and cognitive problems which later progress to dementia. Pigmented retinal degeneration is commonly found. Treatment with pantothenate (vitamin B5) may possibly be beneficial.

Aceruloplasminemia is a rare autosomal recessive disorder occurring mostly in Japan, leading to an absence of ceruloplasmin presenting in adulthood. Abnormal deposition of iron occurs in the pancreas (leading to diabetes), liver, retina and the basal ganglia. The clinical triad of findings consists of retinal degeneration, diabetes mellitus, and neurologic symptoms. Among the latter, movement disorders and ataxia are most common, and cognitive problems leading to dementia occur in ~25%. Treatment is with chelating agents like desferrioxamine.

### Neuroimaging Findings

In PKAN and idiopathic NBIA, iron deposition leads to bilateral low signal intensity in the globus pallidus, to which in later phases gliosis and necrosis are added, leading to central high signal on T2-weighted images. The combination of low signal surrounding an area of high signal in the medial globus pallidus is referred to as the 'eye-of-the-tiger' phenomenon (Fig. 5.52), which is closely associated with mutations in the *PANK2* gene – with apparently all PANK2-mutation–positive patients showing the eye-of-the-tiger sign.

In aceruloplasminemia, areas with low signal on T2*-weighted MRI of the brain due to iron deposition can be found in the basal ganglia (including globus pallidus), midbrain nuclei and dentate. Low signal on all sequences, but especially T2-weighted images, is evident on abdominal MRI scans in visceral organs like the liver, spleen and pancreas (as in secondary haemochromatosis)

### Differential Diagnosis and Work-up

In patients suspected of NBIA, other disorders to consider are MSA and PSP, and Wilson's disease. Beyond genetic testing, diagnosis is based on clinical findings (retinal degeneration, diabetes and neurological findings), laboratory findings (serum copper, ceruloplasmin, and iron), and neuroimaging findings. Especially in those cases where a genetic mutation cannot be found (~50% of NBIA), the combination of clinical and radiological findings is important.

## 5.5.4 Dentatorubral-Pallidoluysian Atrophy

**Synonyms**

Haw River syndrome; Naito-Oyanagi disease

Dentatorubral-pallidoluysian atrophy (DRPLA, OMIM #125370) is an autosomal dominant trinucleotide repeat disorder bearing some similarity to Huntington's disease (HD). It is a rare disorder with most cases having been identified in Japan (prevalence there being ~0.5/100,000). While presentation in younger patients is dominated by myoclonus and epilepsy, adult-onset cases present with ataxia, choreoathetosis, and dementia. Diagnosis is based on clinical findings, family history and genetic testing. Differential diagnosis includes HD and the spinocerebellar ataxias.

DRPLA is characterized neuropathologically by severe generalized brain atrophy. Accumulation of (probably toxic) mutant atrophin-1 leads to intranuclear neuronal inclusions. Atrophy is found in the globus pallidus and subthalamic nucleus

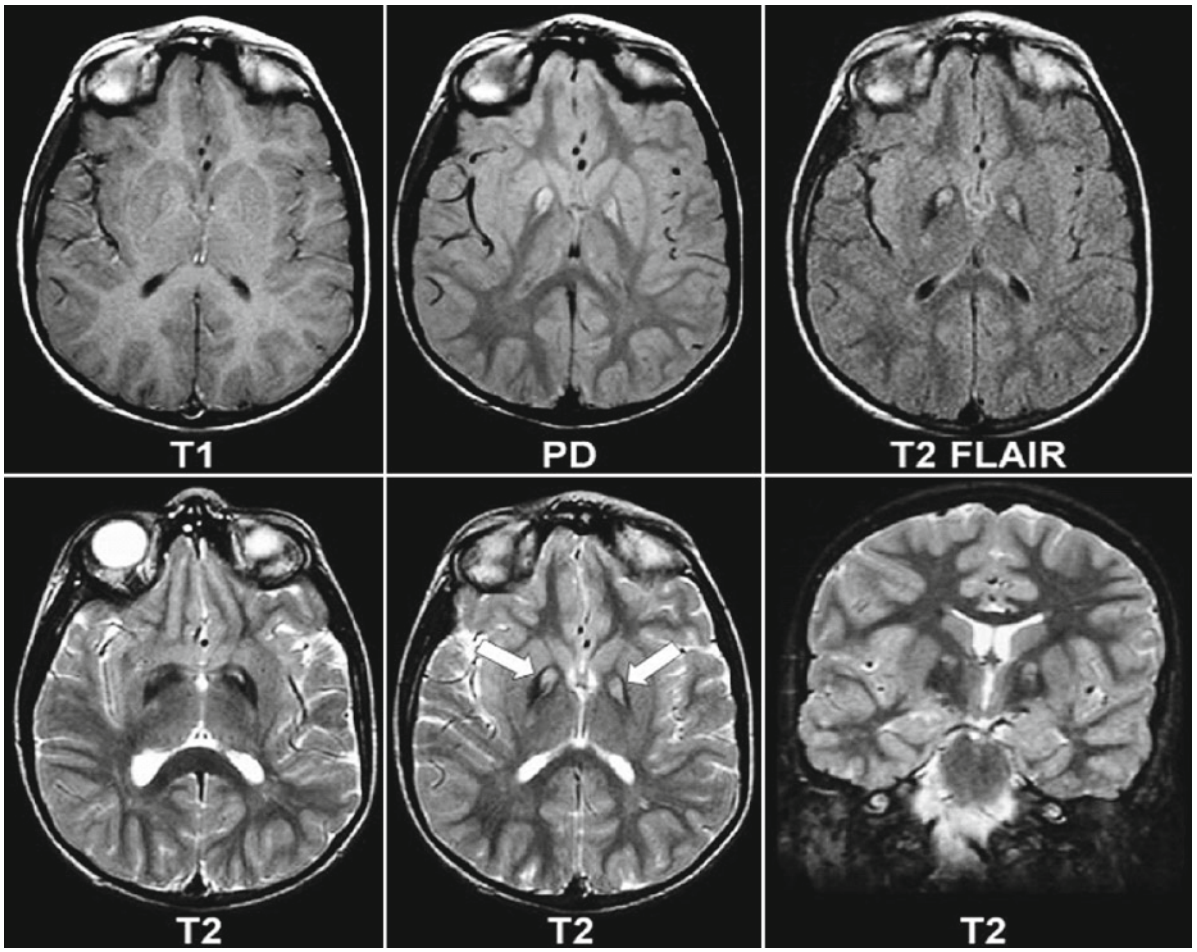



**Fig. 5.52** Eye-of-the-tiger sign. This 10-year-old boy with the PANK2 mutation shows MR features characteristic of PKAN. The T1-weighted images appear normal, but high signal intensity can be seen in the globus pallidus on proton density (PD), FLAIR, and T2-weighted images in both the axial and coronal planes. With increasingly heavier T2 weighting (PD/FLAIR/T2), there is increasingly conspicuous T2 hypointensity at the periphery because of the magnetic susceptibility effects of excess iron, producing the 'eye-of-the-tiger' appearance (*arrows*). (Reprinted with permission from Susan Hayflick (2006 ) AJNR Am J Neuroradiol. Jun–Jul; 27(6):1230–1233)

(also called the Body of Luys) with associated gliosis. Atrophy also occurs in the dentate and red nucleus.

#### 5.5.4.1 Neuroimaging Findings

Atrophic changes on MRI can be found in cerebellum, brainstem and thalamus. The tegmentum of the pons is particularly affected in DRPLA. The age at MRI and the number of CAG repeats correlate with the degree of atrophy – as in other CAG repeat syndromes increase in expansion length occurs in offspring, a phenomenon referred to as anticipation. Diffuse white matter, thalamic and brainstem hyperintensities can be seen on T2-weighted MRI in patients with adult-onset DRPLA of long duration (Fig. 5.53). Intrafamilial heterogeneity of DRPLA is evident on MRI, as is true for the clinical phenotype. Specific changes in the globus pallidus and subthalamic nucleus can be detected only by means of quantitative MRI (ADC mapping) or MR spectroscopy.

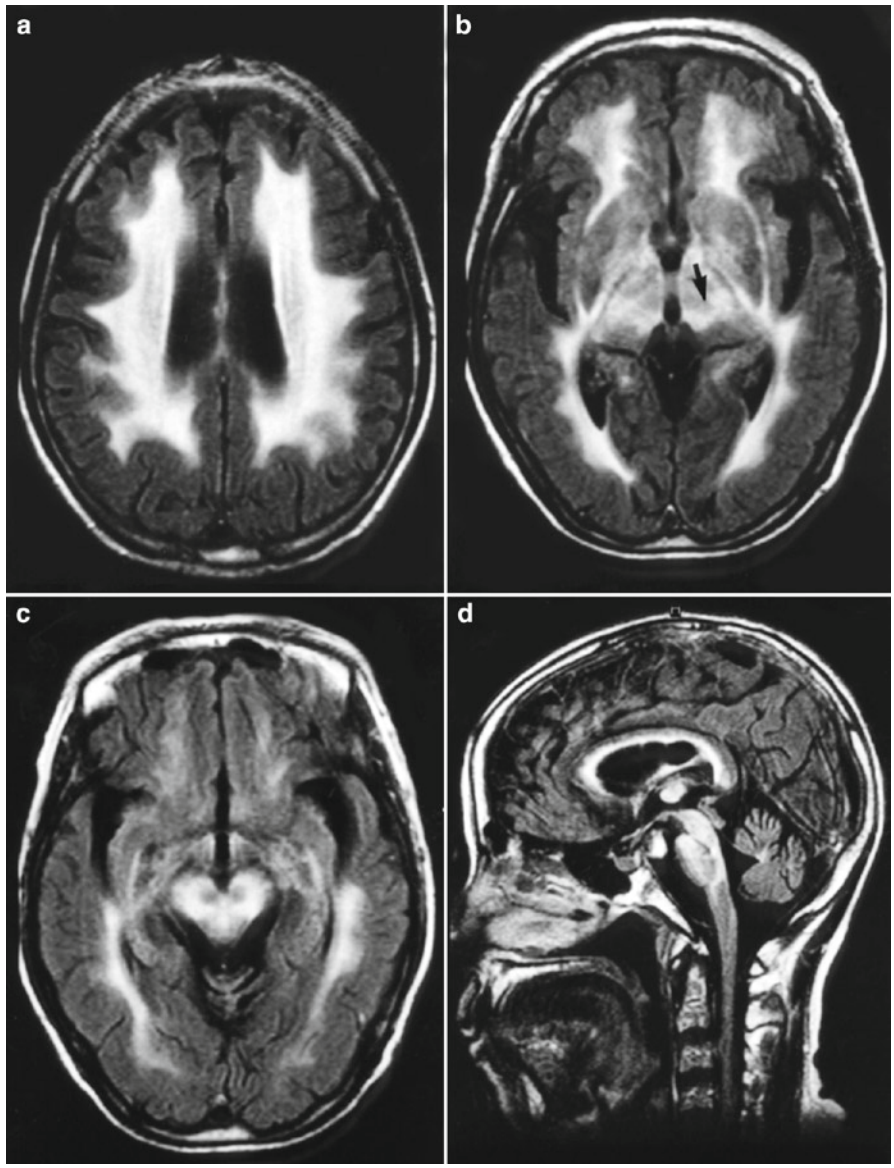



**Fig. 5.53** FLAIR findings in DRPLA. This 60-year-old woman had a family history of DRPLA: the number of CAG repeats in the DRPLA gene on chromosome 12 was expanded to 59 (normal allele 10). Note prominent confluent hyperintensities in the periventricular white matter (**a**), and also the bilateral thalami (**b**, *arrow*), areas that are not commonly involved in DRPLA. In the midbrain, the fasciculi surrounding the red nucleus are remarkably hyperintense (**c**). The sagittal image shows hyperintensities in the corpus callosum, cerebral peduncles, decussation of the superior cerebellar peduncles, and the ventrolateral portions of the mesencephalopontine tegmentum, as well as a central region of the pontine base (**d**). (Reprinted with permission from J Neurol Neurosurg Psychiatry. 1998; 65(3):396–399)

## 5.6 Prion-Linked Dementias

### 5.6.1 *Introduction – History, Nosology and Transmission*

The first transmissible spongiform encephalopathy (TSE) to be recognized was scrapie. This disease of sheep and goats has been known for more than two centuries (the name is derived from the fact that sheep with this disease have a severe itch and scrape off their fleece by rubbing). Icelandic farmers deduced that the disease was infectious and in 1936 scrapie was transmitted by injecting infected sheep brain into uninfected sheep.

The first clinical-pathological description of a TSE in humans was delivered by Jakob (1921), who believed, probably erroneously, that Creutzfeldt had previously described a similar case (1920). The name Creutzfeldt–Jakob disease (CJD) was coined by Spielmayer in 1922. In 1959, Klatzo et al. noted the similarities between the neuropathology seen in CJD and a disease called kuru, a non-inflammatory spongiform encephalopathy found among the Fore people of the eastern highlands of Papua, New Guinea. In 1966,

Gajdusek described transmission of kuru to subhuman primates by intracerebral inoculation of brain tissue, and was awarded the Nobel prize for recognizing this new type of disease in 1976. The proteinaceous infectious particle (PrP) is, in fact, a modified protein ($PrP^{sc}$). The Nobel prize for medicine in 1998 was awarded to Prusiner, who coined the name prion.

TSE constitutes a group of diseases in humans and animals presenting with similar clinical and neuropathological (spongiform encephalopathy) features. Having in common a long incubation period, they were formerly referred to as slow-virus diseases. In humans, TSE include:

| | |
|---|---|
| • Creutzfeld–Jakob disease (CJD) | – Sporadic, familial, and iatrogenic |
| • Variant CJD (vCJD) | – Sporadic (and possibly iatrogenic) |
| • Gerstmann–Sträussler–Scheinker (GSS) disease | – Only familial |
| • Fatal Familial Insomnia (FFI) | – Familial and sporadic |
| • Kuru | – Only sporadic |

In animals, TSE encompasses scrapie, transmissible mink encephalopathy, ungulate spongiform encephalopathy ('Chronic wasting disease' in deer and elk), feline spongiform encephalopathy and bovine spongiform encephalopathy (BSE) or 'mad cow disease'. Some of the animal forms are transmissible to humans, e.g. transmissible mink encephalopathy (USA, Russia, Canada) and BSE. With the advent of vCJD, BSE has become known for its transmission to humans on a relatively large scale, now also beyond the United Kingdom. More recently there has been concern about transmission via blood transfusion from donors who may be incubating vCJD. No treatment exists for any prion disease, but diagnosis is important to prevent transmission.

### 5.6.2 Biochemistry, Genetics and Histopathology

A remarkable feature of human TSE is that both infectious and inherited forms exist. Of all cases of CJD, 15% are inherited in an autosomal dominant way, whereas for GSS syndrome, 100% of cases are inherited. The sporadic, genetic and infectious forms are all due to abnormalities of a 33–35 kDa sialoglycoprotein, the prion protein (PrP). Normal PrP is a cell surface glycoprotein expressed at particularly high levels in nerve cells with unknown function. The infectious particle is composed largely, if not exclusively, of the abnormal isoform $PrP^{sc}$. Normal cellular PrP molecules convert into pathogenic isoforms ($PrP^{sc}$) through configurational changes. There is a post-translational modification of the abnormal $PrP^{sc}$, by formation of an alpha-sheet configuration for a greater part of the molecule with diminished alpha-helical configuration giving rise to four different $PrP^{sc}$ molecular strain types upon Western blot analysis based on type of glycosilation – those subtypes are partly linked with the codon 129 type of homozygosity (M or V).

The prion protein gene maps to the short arm of chromosome 20 and is designated PRNP gene. The methionine to valine (M-V) polymorphism at PRNP codon 129 influences disease expression not only in inherited CJD cases but also in sporadic and iatrogenic forms. In Caucasian patients with sporadic forms of CJD, 95% or more are homozygous for M or V at codon 129. In the normal population the proportions are 12% V/V, 37% M/M and 51% M/V. The vast majority of patients with variant CJD have been M129 homozygous. However, there has been a report of a case of clinically probable vCJD who was heterozygous (MV) at codon 129 – raising the possibility of a second wave of vCJD cases.

Some mutations in the PRNP gene show a close association with particular clinical forms of prion-related disease, but there are also dissociative effects: for example a mutation at codon 178 (replacing asparagine by aspartic acid) in combination with M129 homozygosity is linked to both FFI and a typical CJD syndrome. For unknown reasons, the neuropathology in FFI is largely confined to the mediodorsal and anterior ventral nuclei of the thalamus, whereas in familial CJD the neuropathology is widespread over the cerebral cortex and subcortical nuclei.

GSS syndrome, like CJD, is not a single disease. There are at least six different disorders, each with a separate clinical presentation, neuropathological picture and mutation of the PRNP gene. The codon 102 mutation (P102L) has been linked to the family first

described by Gerstmann, Sträussler and Scheinker. The forms linked to the other mutations were named after this syndrome for the presence of the typical GSS-type multicentric prion protein amyloid plaques.

The main histological abnormality is the vacuolated neuron in scrapie and vacuolation of the neuropil between nerve cells in CJD – hence the name spongiform encephalopathy. The gross appearance of the brain in CJD is variable and not diagnostic. There may be cortical, striatal and cerebellar atrophy, with brain weights usually below normal. Histologically, there is a spectrum of intensity and distribution of lesions, and various subtypes have been distinguished histologically: cortical, cortico-striatal with or without visual loss, cortico-striato-cerebellar, corticospinal and corticonigral. It is assumed that the differences are the result of the different isoforms of PrP involved, although this has not been proven.

The prominent pathological features of CJD are spongiform degeneration of neurons, neuronal loss, intense reactive astrogliosis and amyloid plaque formation; the final proof is abnormal PrP staining. The vacuoles are located in the neuropil between nerve cell bodies. This spongiform degeneration can be found in the cerebral neocortex, the subiculum of the hippocampus, putamen, caudate nucleus, thalamus and the molecular layer of the cerebellar cortex. It is minimal to absent in the globus pallidus, Ammon's horn, and the dentate gyrus of the hippocampus, brainstem and spinal cord. Spongiform degeneration of the cerebral cortex occurs in nearly all cases, regardless of the clinical presentation. The amount of vacuolation can vary widely from region to region. The degree of reactive astrocytosis corresponds well with the loss of nerve cells. In CJD and in the other prion diseases, changes in the white matter are mostly secondary to grey matter changes. Particularly in Japan, however, cases have been described with white matter vacuolation. The vacuoles are within the myelin sheath and occasionally axonal. In a minority of CJD cases (5–10%) amyloid plaques are found. These plaques are immunoreactive with PrP antibodies, but are negative with antibodies to beta-amyloid. In CJD, they consist of spherical masses with radiating amyloid spicules at their periphery and are referred to as 'florid' (kuru) plaques. In the differential diagnosis, presenile (frontotemporal) dementia with motor neuron disease is most important, because in that disease vacuolation of the cerebral cortex is found, whereas in many cases of CJD the lower motor neuron is also involved.

In variant CJD, the findings differ from sporadic CJD. There are numerous florid (kuru-like) amyloid plaques throughout the cerebral and cerebellar cortex, with prominent involvement of the basal ganglia, and posterior nuclei of the thalamus. The amyloid plaques are surrounded by spongiform degeneration. Contrary to sporadic CJD, the lymphoid tissues throughout the body are infected in variant CJD, e.g. the tonsils. In FFI, spongiform lesions are most prominent in the thalamus. In GSS syndrome, bizarre multicentric amyloid plaques are found in the molecular layer of the cerebellar cortex. Plaques can also be found in the basal ganglia and cerebral cortex. The plaques are multicentric with a central larger mass of amyloid surrounded by smaller satellite amyloid deposits. The degree of spongiform changes may be limited, while GSS also features neurofibrillary tangle formation similar to Alzheimer's disease.

## 5.6.3 Creutzfeldt–Jakob Disease

Sporadic CJD accounts for 85% of human prion-related disease. There are some distinctive variants of CJD: the Heidenhain variant with early cortical blindness and prominent occipital atrophy, the Brownell-Oppenheimer variant with severe cerebellar signs and atrophy but little cognitive impairment, the Stern-Garcia variant with extrapyramidal signs due to prominent involvement of the thalamus and basal ganglia presenting; the panencephalitic (Japanese) variant with disproportionate involvement of the white matter; and finally a poliodystrophic form.

### 5.6.3.1 Clinical Presentation, Epidemiology and Treatment

*Sporadic CJD* usually presents in the fifth to seventh decade, but cases with younger and later onset have been described. Worldwide, CJD has an incidence of one per million persons. It is sporadic in 85–90% of cases, inherited in 10–15% of cases and transmissible in less than 5% of cases. The mode of presentation may differ depending on the molecular subtype. The most common (classical) presentation is a triad of

subacute dementia, myoclonus and motor disturbances (extrapyramidal or cerebellar) with a characteristic electroencephalographic (EEG) pattern consisting of triphasic waves, and CSF abnormalities (increased CSF tau and/or 14-3-3 protein, the former being more sensitive). Not all these features need to be present, and CJD should be considered in every patient presenting with a rapidly progressive dementia.

In the early stages of sporadic CJD, the symptoms are often ambiguous, with fatigue, insomnia, restlessness and mild anorexia. In several weeks to months, the second stage follows with cognitive deterioration, cerebellar, behavioural and visual signs. The final stage is akinetic mutism, with an almost silent EEG pattern with 'burst suppression'. Median survival is only ~4 months and most patients die within 2 years of diagnosis (survival is influenced by strain type and PRNP 129 genotype). A definite diagnosis can only be obtained by biopsy, but a probable diagnosis according to WHO criteria can be made on the combination of at least two clinical features and typical EEG or CSF findings.

*Familial prion disease* (*inherited CJD*) accounts for 10–15% of prion disease; point mutations and insertional (repeat) mutations are common and the age at onset varies widely; disease duration is usually longer than in sporadic CJD. Particular phenotypes include fatal familial insomnia (FFI) and Gerstmann–Straussler–Scheinker disease (GSS) described below. Patients with familial prion disease may also resemble familial AD or sporadic CJD.

*Iatrogenic CJD* may occur through tissue transfer (e.g. dura mater grafts or cadaveric human growth hormone) or via contaminated instruments used in cerebral operations (e.g. intracerebral electrodes). The incidence of iatrogenic CJD has fallen since the 1990s; remaining cases are due to long incubation periods (up to 40 years). The recent discovery of transfusion-associated variant CJD infections has provoked new concerns about the possibility of further secondary transmissions from operative procedures, blood transfusions and tissue donations.

*Variant CJD* is a new form of CJD that is associated with BSE, with a very different presentation and different histopathology. Clinical presentation includes prominent psychiatric features at onset, soon followed by dementia but lacking cerebellar signs and occurring at a young age (median age 29 years) and having a longer survival. The salient differences between sporadic and vCJD are summarized in Table 5.15.

#### 5.6.3.2 Imaging Strategy and Findings

The first line of investigation in patients suspected of CJD is MRI, including diffusion-weighted imaging (DWI); images after contrast-material administration

**Table 5.15** Clinical and MRI findings distinguishing Classic CJD from Variant CJD

| Characteristic | Classic CJD | Variant CJD |
|---|---|---|
| Median age at death | 68 years | 28 years |
| Median duration of illness | 4–5 months | 13–14 months |
| Clinical signs and symptoms | Dementia; early neurologic signs | Prominent psychiatric/behavioural symptoms; painful dysaesthesiasis; delayed neurologic signs |
| Periodic sharp waves on EEG | Often present | Often absent |
| Presence of agent in lymphoid tissue | Not readily detected | Readily detected (tonsillar biopsy is a useful diagnostic procedure) |
| 'Pulvinar sign' on MRI on FLAIR/DWI | Rarely | Present in >75% of cases |
| Caudate/putamen signal on FLAIR/DWI greater than thalamus | | Characteristic – unilateral or bilateral |
| Diffusion changes in neocortex | | Often – multifocal |

*Source*: Adapted from Belay E, Schonberger L (2002). Variant Creutzfeldt-Jakob Disease and Bovine Spongiform Encephalopathy. Clin Lab Med 22:849–862

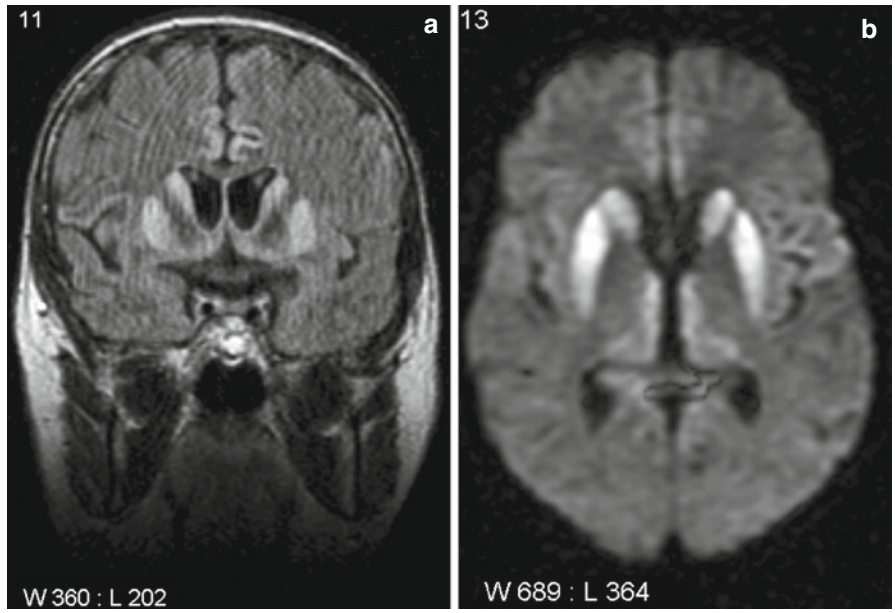



**Fig. 5.54** CJD with striatal involvement. This young man developed iatrogenic CJD more than 10 years after receiving human growth hormone. The coronal FLAIR (*left*) and axial diffusion imaging (B1000 – *right*) shows marked striatal involvement characteristic of sCJD and iatrogenic CJD

are only useful to rule out alternative disorders. Conventional T2-weighted and especially FLAIR sequences may show increased signal in the striatum, especially the putamen (Fig. 5.54) or the neocortex. However, in up to 20% of cases no abnormal signal is found and a normal conventional MR scan thus does not rule out CJD and may demand the use of other sequences, such as DWI to show striatal or cortical involvement. Abnormal DWI may be especially prominent in early phases of the disease when vacuoles are small, leading to restricted diffusion (which may disappear in late stages). Contrast injection should be performed to rule out other disorders, but will usually not give new information in CJD itself. If the initial imaging is negative, repeat MRI after several weeks is indicated, with emphasis on DWI (which may be progressively abnormal in prion disease).

In spongiform encephalopathies, the patterns of selective involvement of cerebral structures include involvement of either basal ganglia (caudate and putamen – Fig. 5.54), thalamus (medial and dorsal parts) or widespread, irregular involvement of the cerebral cortex (Box 5.6). Sometimes, there is a combination of neocortical and subcortical involvement. Usually, the pattern of involvement is bilateral, but it may be unilateral as well (initially). In sporadic (and iatrogenic) CJD, involvement of either the striatum (Fig. 5.54) or neocortex (Fig. 5.55) or both is found, with possible determination of the imaging pattern based on the PrP subtype. In vCJD, there is selective involvement of the medial and dorsal (pulvinar) thalamic nuclei, leading to the so-called hockey-stick sign (Fig. 5.56). This pulvinar sign has high sensitivity and specificity for the diagnosis of vCJD. Some atypical cases of probable sporadic CJD with a pulvinar sign have been reported (Fig. 5.57), and the combination of abnormalities may become more evident when DWI is obtained using higher B-values than normal (Fig. 5.58). MR spectroscopy is non-specific, and only in the later phases shows the pattern of brain damage, with lowering of the metabolites, especially N-acetylaspartate, with sometimes high myo-inositol. SPECT may reveal non-specific areas of lower tracer uptake in neocortical areas, with limited specificity.

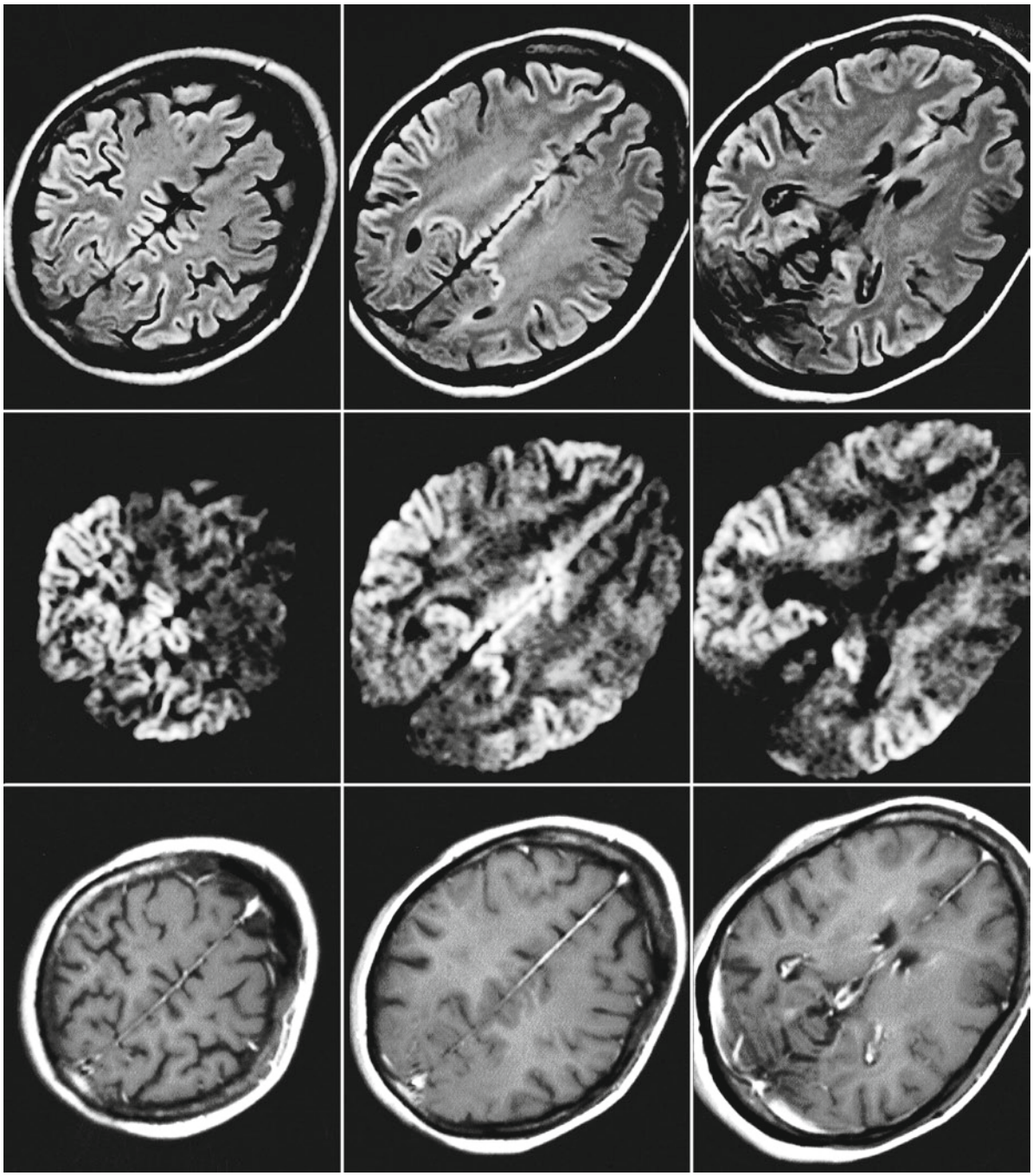


**Fig. 5.55** This 39-year-old woman presented with rapid deterioration over half a year, with agitation, hyperactivity, confusion and was initially diagnosed as a psychiatric disorder. EEG findings, CSF analysis and abnormal MRI findings led to the diagnosis of sCJD. Note the increased signal of multiple cortical areas on FLAIR (*top row*) which are more conspicuous on DWI (*middle row*). As expected there was no enhancement with gadolinium (*bottom row*)

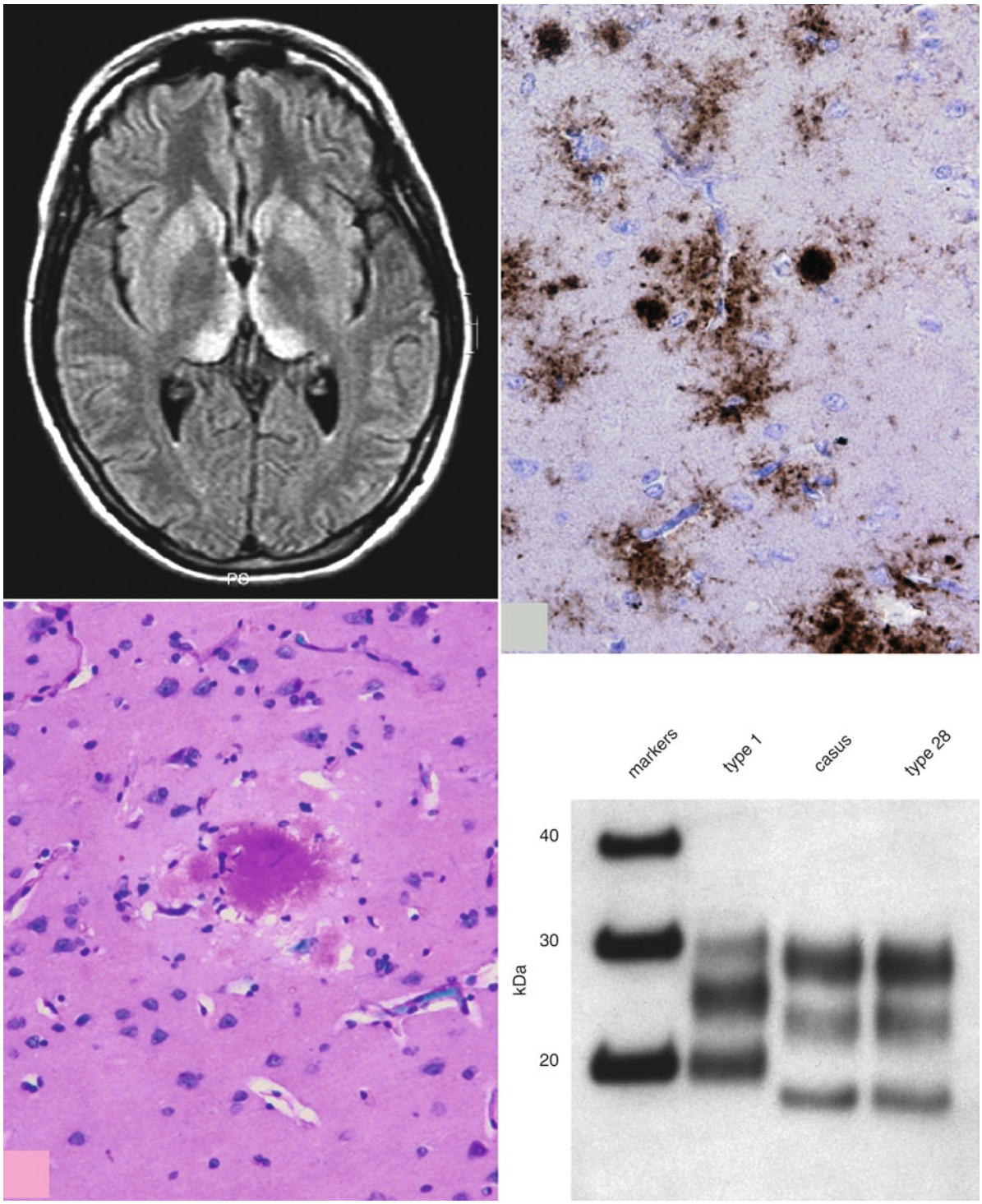



**Fig. 5.56** Pulvinar sign in vCJD. A Dutch woman died at the age of 26 years, after a disease duration of 18 months, due to variant CJD. She had never travelled to the UK and there was no history of potential iatrogenic exposure. However, she had worked in the catering and food production industry for the previous 6 years and had frequently consumed raw meat. The disease course showed the classical clinical picture of vCJD, with high signal on FLAIR in the pulvinar on MRI (*upper left*). Postmortem examination of the brain showed florid plaques with surrounding spongiform changes (*lower left*) and marked immunoreactivity for prion protein (*upper right*). Western blot analysis revealed a protease-resistant prion protein with a glycosylation pattern similar to variant CJD (type 2B) and dissimilar to sporadic CJD (type 1) (Reprinted with permission from Ned Tijdschr Geneeskd 2005;149:2949–2954)

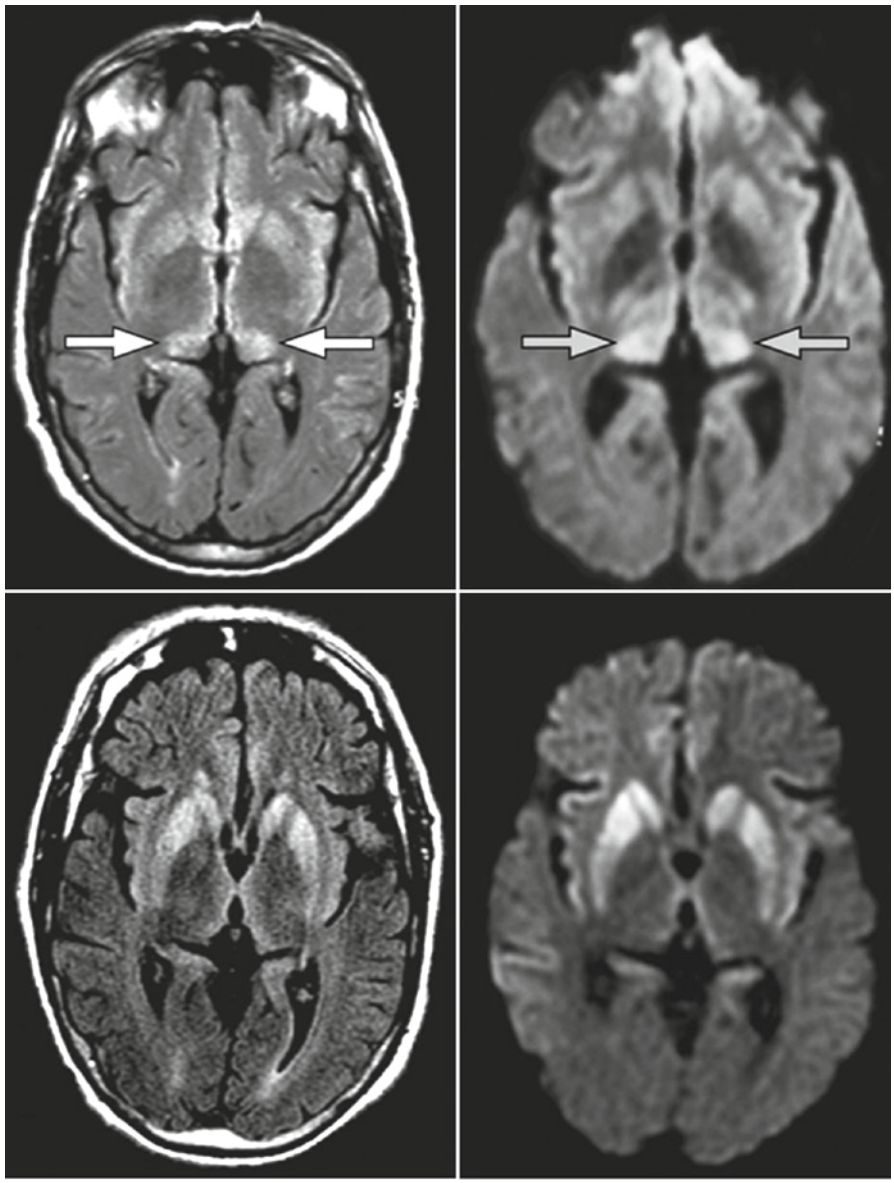


**Fig. 5.57** Pulvinar sign in sporadic CJD. Fluid-attenuated inversion recovery (**a**) and diffusion-weighted imaging (**b**) showing a typical pulvinar sign (*arrows*) in a 64-year-old man with a final clinical diagnosis of sporadic CJD. He was initially thought to have possible variant CJD but had a negative tonsillar biopsy. The same imaging 7 months later (**c** and **d**) shows increased signal intensity in the striata bilaterally and disappearance of the pulvinar sign. (Reprinted with permission from Lancet 2010; 375:889–890)

## Box 5.6 Key imaging findings in prion disease

| | |
|---|---|
| Sporadic CJD | Abnormal signal on FLAIR/DWI<br>(a) Caudate and putamen signal increase<br>(b) Widespread (patchy, ribbon-like) neocortical signal increase<br>(c) A combination of the above |
| Variant CJD | Thalamic hockey-stick or pulvinar sign on FLAIR/DWI |
| GSS | Abnormal MRI signal in striatum, thalamus or cortex |
| FFI | Normal MRI and reduced thalamic FDG uptake on PET |

... No contrast enhancement in any ...

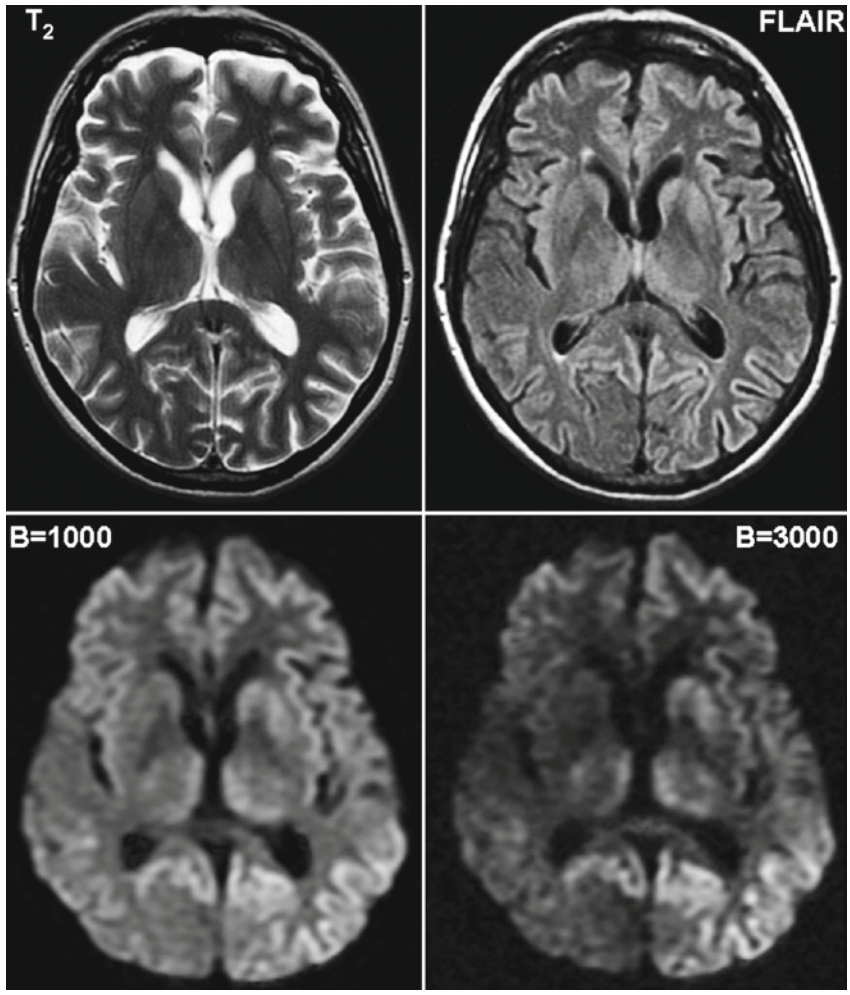



**Fig. 5.58** Comparison of imaging features with different pulse-sequences in a case of sporadic CJD. Note that the mixed pattern of neocortical, thalamic and striatal involvement becomes more prominent on DWI with higher than usual B-values (3,000 rather than 1,000 s/mm$^2$). (Images kindly provided by Harpreet Hyare, UCL)

#### 5.6.3.3 Differential Diagnosis and Ancillary Investigations

In patients with a rapidly progressive dementia, several conditions need to be considered, including vasculitis, limbic encephalitis, infections and malignancy. Other degenerative conditions include FTLD with motor-neuron disease and also atypical AD and DLB. Laboratory or other findings that can be helpful include:

- Periodic sharp waves on EEG
  - Also found in herpes encephalitis, SSPE
  - Can be introduced by drugs
  - Lithium, valproate and tricyclic antidepressants
  - Occur in metabolic and post-hypoxic disorders
- 14-3-3 protein is present in the CSF in >90% of sporadic CJD cases
  - Only in ~50% of variant cases
  - Also found in other rapidly progressive neurodegenerative disorders, including AD
- CSF tau is often markedly (>2,000 pmol/l) raised in CJD
  - Much more than in other disorders, e.g. AD
- Tonsilar biopsy in variant CJD shows prion staining
- Brain biopsy may be needed to exclude cerebral vasculitis

MRI abnormalities, especially abnormal DWI probably antedate the onset of typical EEG findings. A pattern of multifocal neocortical DWI abnormalities can be found in mitochondrial disease (e.g. MELAS), herpes infection, venous congestion due

to arteriovenous fistula, and perhaps rapidly progressive AD as well.

### 5.6.4 Gerstmann–Sträussler–Scheinker (GSS) Syndrome

GSS syndrome is a rare familial prion disease. It was first described in a Viennese family in 1936. All cases are inherited via an autosomal dominant mode of inheritance. Worldwide more than 30 families have now been recognized with the disease. Clinically, GSS syndrome presents in the fourth to sixth decades and shows a slow progression over about 6 years. The major symptoms are difficulty in walking and unsteadiness, with variable leg pain and paraesthesias in the early stages, later followed by mental and behavioural deterioration, ataxia and dysarthria.

MRI may only show non-specific atrophy and abnormal signal on DWI in the cortex and striatum, as in sporadic CJD, but also the thalamus. Serial MRI may show progressive cerebellar atrophy as well as cortical loss (Fig. 5.59). Reduced NAA has been reported in spectra from the frontal lobe and cerebellum. SPECT may show reduced tracer uptake, though not in the expected cerebellar location. EEG shows non-specific changes, and 14-3-3 protein is usually absent in CSF.

### 5.6.5 Fatal Familial Insomnia (FFI)

FFI is an autosomal dominant inherited form of (thalamic) dementia, with some pathological features of CJD. Insomnia, rather than dementia, is the prominent clinical symptom, although this feature may be difficult to apprehend since patients may show excessive daytime sleepiness. A wide variety of neurological features, both pyramidal and extrapyramidal, may occur and the course is fatal in a short period of time. Sporadic cases of FFI occur as well.

MRI may show non-specific atrophy, but no abnormal signal, even in the thalamus. Similarly, EEG shows non-specific alterations and the CSF is negative for 14-3-3 protein. PET is especially important in the diagnosis of FFI, with absent thalamic uptake despite normal appearance on MRI – a finding that is virtually pathognomonic (Fig. 5.60).

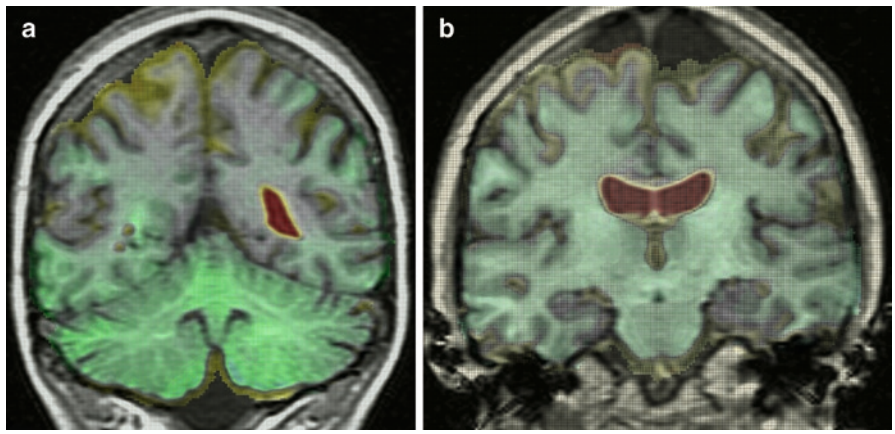



**Fig. 5.59** Colour overlay image of fluid-registered serial MRI (2 years apart) of familial prion (GSS) case. This 42-year-old woman with a family history of dementia developed balance problems, a broad-based ataxic gait, dysarthria and minor subtle cognitive and behavioural problems. Hereditary prion dementia (GSS) was confirmed by finding a point mutation at codon 102 of the prion protein gene (PrP Leu 102). The fluid overlays are from two scans spanning symptom onset (the first was acquired when the patient was asymptomatic as part of a research study in at-risk individuals) The figure shows diffuse atrophy involving (**a**) cerebellum, but (**b**) clear preservation of hippocampi (areas of loss are shown in blue/green and areas of expansion are shown in red/yellow e.g. ventricular expansion)

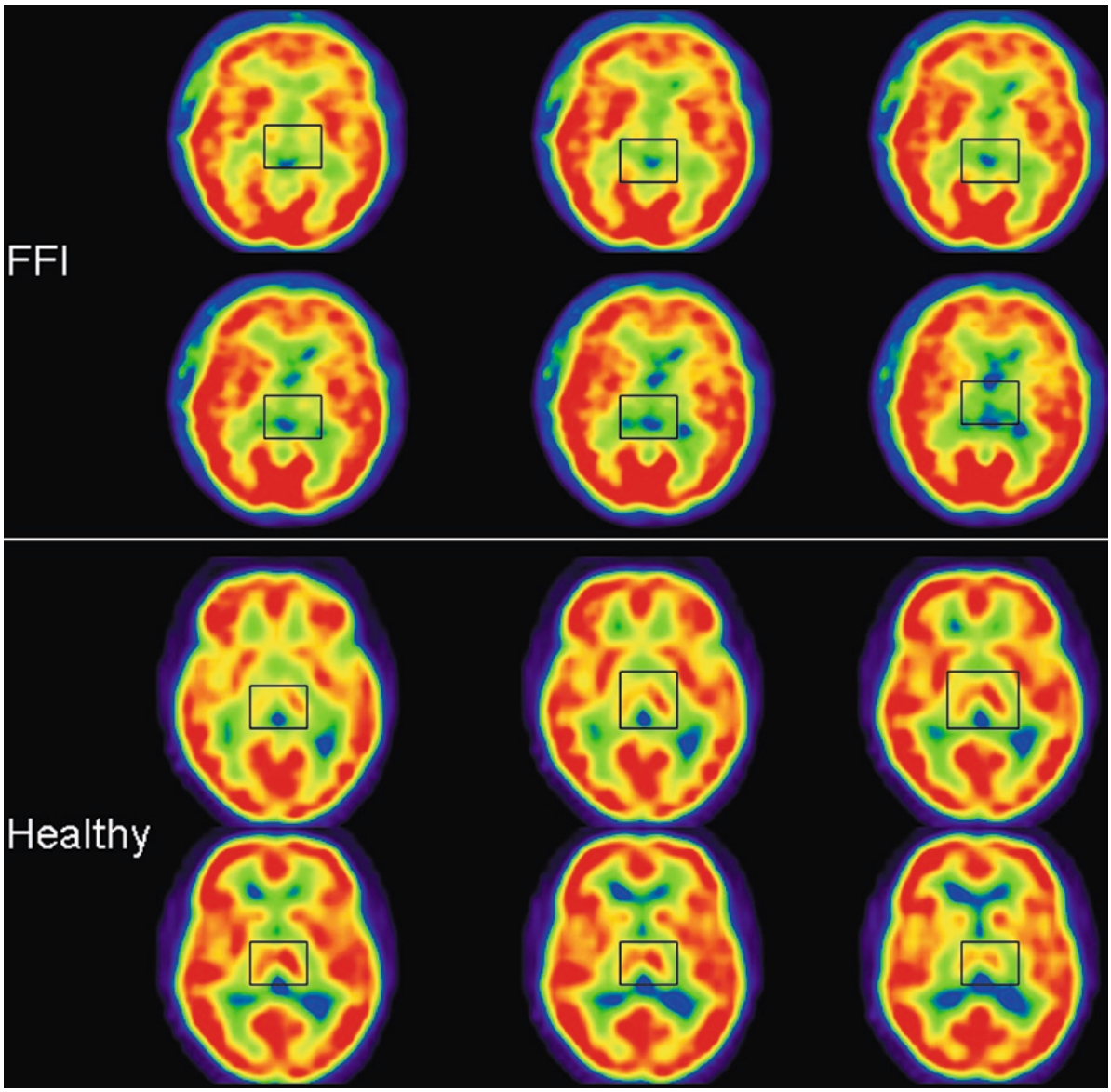



**Fig. 5.60** Thalamic hypometabolism in sporadic FFI. FDG-PET images of a 40-year-old male patient who presented with excessive daytime sleepiness, because of nocturnal insomnia that was discovered only later, followed by progressive neurological deficits, such as pyramidal and extrapyramidal features, severe aphasia and ultimately mutism. Tonsillar biopsy was negative. FDG-PET revealed strongly reduced thalamic tracer uptake consistent with FFI (*upper rows*). For comparison, note normal metabolism in the thalamus in a healthy control (*lower rows*)

## 5.7 Recreational Drugs and Alcohol

### *5.7.1 Introduction*

There are many recreational drugs that have an impact on the central nervous system beyond their presumed recreational effects. In this chapter, we focus on the grey matter damage caused by two more commonly used drugs, ecstasy and alcohol. Some effects of recreational drugs manifest as white matter disease in the brain: Wernicke-Korsakoff syndrome due to B1-deficiency, Machiafavi–Bignami disease and heroin-induced leukencephalopathy. Those disorders will

be discussed in Chap. 7. The main findings in recreational substance abuse include:

| |
|---|
| Alcohol<br>• Global brain atrophy<br>• (Hypo)thalamic changes in Wernicke–Korsakoff syndrome<br>• Cerebellar atrophy<br>• Corpus callosum changes in Machiafavi–Bignami disease |
| Cannabis, XTC, etc.<br>• Hippocampal and amygdala atrophy |
| Smoking<br>• Non-specific white matter lesions<br>• Reduced grey matter density |

## 5.7.2 Alcohol-Induced Dementia

The effect of alcohol on the brain is partly controversial. Population-based studies suggest a possible beneficial effect of moderate alcohol intake on the brain through positive effects on the cardiovascular system – it is even suggested that onset of AD may be delayed. Excessive intake of alcohol over longer periods of time clearly leads to neurological damage and eventually dementia. Memory loss is a central feature of both the Wernicke-Korsakoff syndrome and alcohol-induced dementia. The differential diagnosis between these two entities is possible using neuropsychological testing, with Wernicke-Korsakoff patients having isolated disturbances in encoding, while alcohol-dementia patients display a more global cognitive decline. Diagnosis of alcohol-induced dementia has been operationalised in the DSM-IV (Box 5.7).

**Box 5.7 DSM-IV criteria for alcohol-induced persistent dementia**

1. The development of multiple cognitive deficits manifested by both:
   (a) Memory impairment (impaired ability to learn new information or to recall previously learned information)
   (b) One (or more) of the following cognitive disturbances
      - Aphasia (language disturbance)
      - Apraxia (impaired ability to carry out motor activities despite intact motor function)
      - Agnosia (failure to recognize or identify objects despite intact sensory function)
      - Disturbance in executive functioning (i.e. planning, organizing, sequencing, abstracting)
2. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning
3. The deficits do not occur exclusively during the course of a delirium and persist beyond the usual duration of substance intoxication or withdrawal
4. There is evidence from the history, physical examination or laboratory findings that deficits are etiologically related to the persisting effects of substance use (e.g. a drug of abuse, a medication)

### 5.7.2.1 Imaging Findings in Alcohol Abuse

Intake of alcohol has several effects on the brain, which are partly reversible. Following abstinence, an increase in brain volume has been found (1–2%), with an increase in NAA in spectroscopy, signifying that alcohol-induced changes are partly reversible (Fig. 5.61a). In the long run, irreversible atrophy occurs, with a particular vulnerability of the brainstem, cerebellum, hippocampus, thalamus and frontal lobes (Fig. 5.61b). The findings related to Wernicke-Korsakoff syndrome due to thiamine deficiency are discussed in detail in Chap. 7.5.2, and include high signal lesion in medial thalamus, mamillary bodies and midbrain.

## 5.7.3 Marchiafava–Bignami Disease

Marchiafava–Bignami disease is a rare complication of chronic alcohol consumption and is characterised by primary demyelination and necrosis of the central part of the corpus callosum. Clinical features include

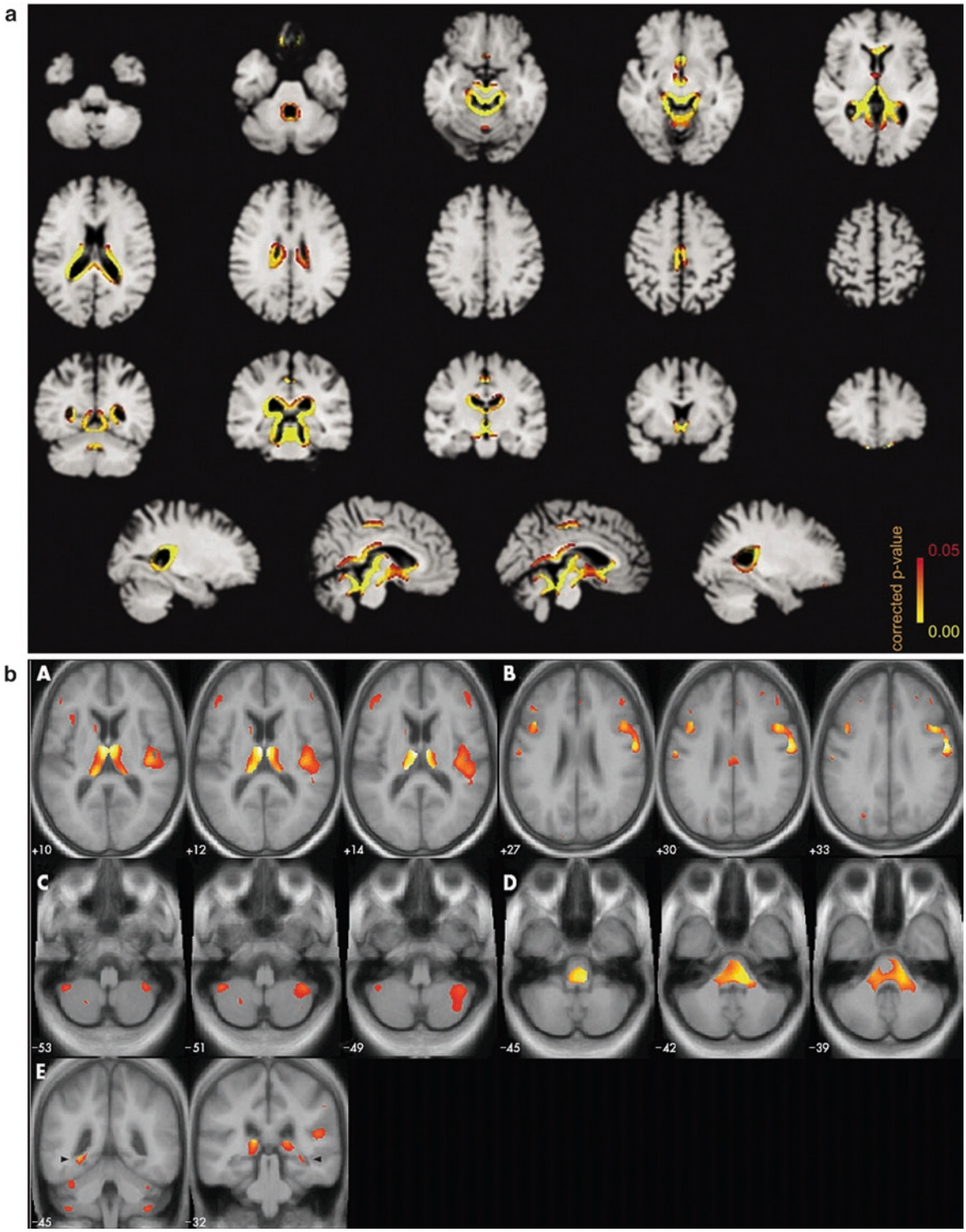



**Fig. 5.61** **(a)** Increase in brain volume (*yellow*) following withdrawal in chronic alcoholics. (Reproduced with permission from Bartsch et al. 2007). (**b**) VBM study of brain volume loss in chronic alcoholism. Changes are most prominent in thalamus and brainstem. (Reproduced with permission from Mechtcheriakov et al. 2007)

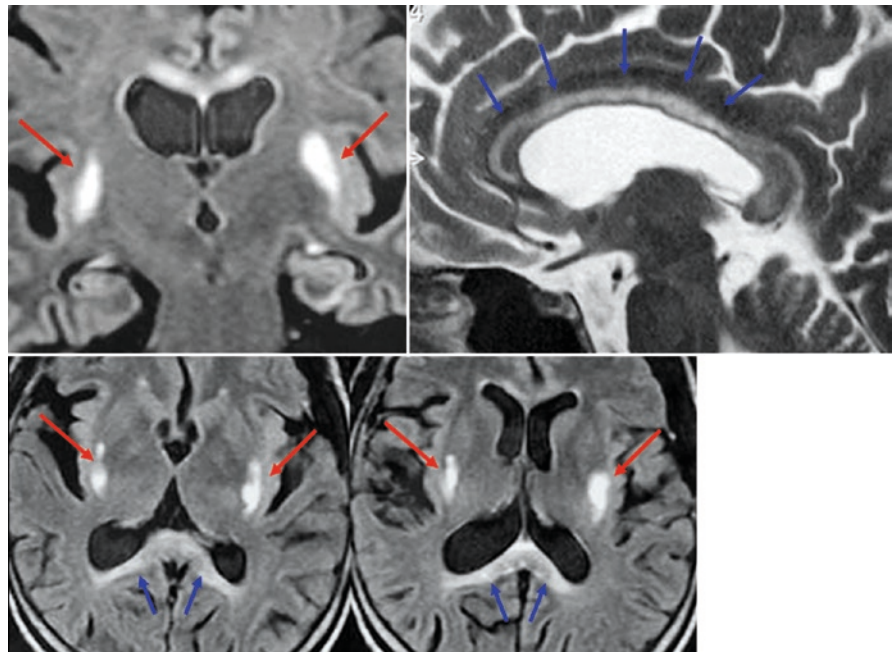


**Fig. 5.62** Marchiafava–Bignami disease. Classic finding of layered necrosis, degeneration and cystic cavitations of the corpus callosum (*blue arrows*). In addition, extensive involvement of the dorsal part of the external capsule (*red arrows*) was seen in this patient. (With permission from Geibprasert et al. 2009 Eur Radiology)

a variety of cognitive and systemic neurological features. Although the true aetiology of this rare condition is still unknown, toxic agents in low quality red wine and/or vitamin B complex deficiencies have been put forward as potential causes. The characteristic MR imaging findings are high T2 signal without significant mass effect within the corpus callosum, which may extend to the genu and adjacent white matter (Fig. 5.62).

### 5.7.4 Cannabis, Ecstasy and Cocaine

Cannabis (active ingredient Δ9-tetrahydrocannabinol or THC) is often considered to be a harmless stimulant and widely used for recreational purposes. In animal studies, however, cannabis has a neurotoxic effect, especially to the hippocampus. Neuroimaging studies on the effect of cannabis in the brain have yielded conflicting results, but do suggest that hippocampal and amygdalar volumes in heavy cannabis users (who are not polydrug addicts) are reduced. Such a reduction may not only affect memory, but also lower the threshold for psychosis. In fact, in patients with schizophrenia, the rate of grey matter decrease, compared to controls, is most marked in those who use cannabis.

Ecstasy (active ingredient 3, 4-methylenedioxymethamphetamine or MDMA) is also widely used for recreational purposes. In animal studies, MDMA causes damage to axons of serotonergic cells. Neuroimaging studies on this relatively novel drug are scarce and confounded by polydrug usage. In frequent users, reduced serotonergic activity has been found using SPECT, while more widespread damage in grey and white matter have been found using diffusion tensor imaging.

### 5.7.5 Nicotine

More than 3 decades of research indicates that smoking has both acute and chronic effects on cognition. Difficulty in concentrating is part of nicotine withdrawal and a likely barrier to success in smoking cessation attempts; most of the neuropsychological research using fMRI has focused on cognitive domains generally classified as ‘executive functions’ including sustained attention and working memory. Studies of smoking abstinence have identified functional brain correlates of increased reactivity to smoking-related cues, and worsening of concentration.

Smoking has not been identified as a cause of dementia, but being a significant cardiovascular risk

factor, smoking has been associated with white matter changes on MRI in many population and clinical studies.

Structural MRI studies comparing smokers and non-smokers indicate that smokers have reduced grey matter volume and density in prefrontal cortical areas involved in executive function. Research on the effects of smoking a cigarette confirms that smoking leads to the release of dopamine in brain reward areas and to nicotinic receptor binding. Smokers' and non-smokers' brains have also been shown to differ in the distribution of nicotinic receptors. Among nicotine-naïve individuals, the $\alpha 4\beta 2$ nicotine receptor has high densities in thalamus, followed by midbrain, pons, cerebellum and cortex. Comparisons of non-smokers and recently abstinent smokers using SPECT/PET show that smokers have higher densities of $\alpha 4\beta 2$ nicotinic receptors both in cerebral cortex and in striatum. Finally, compared to non-smokers, smokers have lower levels of brain monoamine oxidase (MAO). These lower levels of MAO are thought to be due to the ingestion of MAO-inhibiting compounds in cigarette smoke and may play a role – either independently or in synergy with nicotine – in smoking reinforcement.

## Suggested Reading

### Alzheimer's Disease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