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PICTORIAL ESSAY

Neuroradiology of Non-Alzheimer's Disease Dementias

YL Dai[1], K Wang[1], TCY Cheung[1], DLK Dai[2]

[1]Department of Imaging and Interventional Radiology, Prince of Wales Hospital, The Chinese University of Hong Kong; [2]Department of Medicine and Therapeutics, Prince of Wales Hospital, Hospital Authority, Hong Kong

ABSTRACT

Dementia is an increasingly prevalent disease of the ageing population. Although Alzheimer's disease is still the most common cause of dementia, there is emerging clinical interest in other, less common, causes of dementia that can affect patients at a younger age. Early diagnosis of these non-Alzheimer's disease dementias is now possible with the aid of neuroimaging, including computed tomography and magnetic resonance imaging, as well as newer modalities such as magnetic resonance spectroscopy, diffusion tensor imaging, and single-photon emission computed tomography. The imaging features of some of the more common non-Alzheimer's disease dementias will be discussed in this review in order to help clinicians and radiologists better diagnose these conditions.

Key Words: *Alzheimer disease; Aphasia, primary progressive; Dementia, vascular; Magnetic resonance spectroscopy; Multiple system atrophy*

中文摘要

非阿爾茨海默病癡呆症的神經放射學

戴毓玲、王琪、張智欣、戴樂群

隨着人口老化，老年癡呆症患者愈發普遍。雖然阿爾茨海默氏症仍然是老年癡呆症最常見的病因，但臨床對於更年輕患者的其他較少見的病因頗有興趣。神經影像技術有助於非阿爾茨海默氏病的癡呆症的早期診斷，包括電腦斷層掃描和磁共振成像，以及較新型的技術如磁共振波譜、彌散張量成像和單光子發射電腦斷層掃描。本文討論一些較常見的非阿爾茨海默病癡呆症的影像學特徵，以幫助臨床醫生和放射科醫生更好地診斷此類病症。

INTRODUCTION

The prevalence of dementia in people aged 60 years or older in Hong Kong in 2009 was 7.2% and is expected to further increase with the ageing population.[1] Imaging for dementia has long progressed from exclusion of focal brain lesions and identifying surgically rectifiable causes, such as chronic subdural haematomas, to arriving at a specific antemortem diagnosis that has a profound impact on clinical management and prognostic value. Alzheimer's disease (AD) is still the most

Correspondence: *Dr K Wang, Department of Imaging and Interventional Radiology, Prince of Wales Hospital, Shatin, Hong Kong. Email: kwang@ha.org.hk*

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common cause of dementia (50-80% of dementias), with a prevalence of one (13%) in eight people older than 65 years and nearly half (45%) of people older than 85 years. However, less common, but important, causes of dementia such as frontotemporal dementia (FTD) and Lewy body dementia can be diagnosed earlier with brain imaging, especially since patients with these diseases tend to present at a younger age. Rare causes of dementia such as Creutzfeldt-Jakob disease are not included in this article because it is not possible to comprehensively cover all the different types of dementia.

There is increasing clinical interest in identifying and investigating patients with mild cognitive impairment (MCI), which is regarded as a pre-dementia condition with a high risk of progression to dementia within 1 to 2 years. MCI is defined as cognitive decline greater than expected for an individual's age, but which does not interfere notably with daily life. Computed tomography (CT) of the brain is still the most commonly employed first-line investigation for dementia diagnosis, but more advanced imaging modalities such as magnetic resonance imaging (MRI; structural, MR spectroscopy [MRS], and diffusion tensor imaging) and single-photon emission computed tomography (SPECT) are increasingly utilised to provide adjunct information.[2]

Currently, most routine reports for CT of the brain include a comment on the degree of cerebral atrophy, which fails to differentiate between the different types of dementia. An ideal report for dementia diagnosis should aim to provide evidence to support the clinical provisional diagnosis, or exclude some of the differential diagnoses. The report should also suggest whether further investigation such as SPECT or MRI is indicated for management.

COMPUTED TOMOGRAPHY OF THE BRAIN

CT of the brain is a first-line investigation that is used to exclude surgically treatable and reversible causes of dementia, such as chronic subdural haemorrhages and normal-pressure hydrocephalus. Subsequent careful scrutiny of the axial, coronal, and sagittal reformats of the scan is important to look for a specific pattern and distribution of atrophy, for example coronal reformat for assessment and comparison of the contralateral temporal and occipital lobes; and sagittal reformat for comparing the frontal versus parietal lobes and for assessment of the corpus callosum and brainstem. It is inevitable that there will be some degree of cerebral involution with ageing, but the earliest or dominant lobe showing atrophy should be identified. Precise naming of the involved lobar anatomy is preferred over non-specific regions, for example inferior parietal lobe instead of parieto-occipital region. Certain patterns of cerebral atrophy have been associated with different types of dementia (Table 1).

MAGNETIC RESONANCE IMAGING OF THE BRAIN

Structural MRI of the brain is useful to look for atrophy of specific structures. The imaging sequences included in our MCI / dementia examination are listed in Table 2. Apart from excluding gross morphological lesions such as a tumour or subdural collections, we routinely comment on the presence of infarcts and any white matter change, which may suggest underlying chronic small vessel disease and vascular dementia (VaD). The National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et

Table 1. Patterns of cerebral atrophy and related pathologies.

Pattern of atrophy	Pathology
Hippocampal atrophy	Alzheimer's disease
Temporal ± parietal lobe atrophy	Alzheimer's disease
Superior parietal lobe atrophy	Posterior cortical atrophy of Alzheimer's disease
Occipital lobe atrophy	Lewy body dementia
Left perisylvian atrophy	PPA
Midbrain and pons atrophy	Multisystem atrophy
	Progressive supranuclear palsy
Asymmetrical cerebral atrophy	FTD
	CBD
	3 in 1 syndrome (FTD, CBD, PPA)
Disproportionate ventriculomegaly with generalised mild cerebral atrophy	Normal-pressure hydrocephalus

Abbreviations: CBD = corticobasal degeneration; FTD = frontotemporal dementia; PPA = primary progressive aphasia.

l'Enseignement en Neurosciences (NINDS-AIREN) criteria for VaD include findings of multiple large vessel infarcts; single strategically placed infarct; multiple basal ganglia and white matter lacunes; extensive periventricular white matter lesions; or a combination.[3] The pattern of cortical atrophy is readily commented on for MRI. The hippocampus is also carefully scrutinised on the oblique coronal sequence for atrophy, which points towards AD. Thinning of the corpus callosum has been reported in patients with FTD, progressive supranuclear palsy (PSP), and AD.[4-6] We also routinely perform a time-of-flight MR angiography to examine the cerebral vessels for any stenosis or occlusion. The routine reporting template employed in our institution is shown in Table 3.

Proton MRS is also performed in our centre to identify early biochemical disturbances of neuronal metabolites that predate specific atrophy patterns (1.5T; Siemens, Munich, Germany), using 30 ms echo time, 2 x 2 x 2 cm single voxel centred at the right and left posterior cingulate gyri, by the LCModel software (Stephen Provencher Inc., Oakville [ON], Canada) for post-processing.[7] MRS is also useful for patients with mild and non-specific atrophy patterns as it helps to differentiate between physiological age-related involution and pathological MCI, which carries a high risk of progression into dementia. Isolated interpretation of MRS values is not recommended due to the wide range of overlap between different types of dementia, and MRS values should always be interpreted in conjunction with the overall morphological impression, although it is sometimes possible to differentiate FTD from AD using MRS.[8] In general, reduced N-acetyl aspartate/creatine (Cr) ratio reflects loss of neuronal mass and is indicative of pathological MCI, whereas a raised myoinositol/Cr ratio indicates increased glial content and has been shown to be increased in AD (Table 4[9]).

Ultimately, it is extremely important that clinicians provide sufficient and appropriate clinical information. It is essential to ascertain whether the predominant symptoms are related to memory, behaviour / psychology, or speech. The presence of behavioural and psychological symptoms raises the suspicion for FTD so the frontal and temporal lobes should be carefully assessed for atrophy. The presence of speech problems early in the course of the disease prompts suspicion for primary progressive aphasia (PPA) and alerts the radiologist to look for asymmetrical perisylvian atrophy. The clinical constellation of cognitive impairment, visual hallucination, rapid eye movement sleep disorder, and parkinsonism suggestive of Lewy body dementia, and the presence of any occipital atrophy should be stressed if present. It has been shown in previous studies that specific atrophy patterns are usually readily identified by radiologists, but the diagnosis of organic causes of dementia are infrequently proposed in

Table 2. Routine magnetic resonance imaging sequences for mild cognitive impairment / dementia protocol.

Sequence	Magnetic resonance imaging
1	Axial T1-weighted
2	Axial T2-weighted
3	Axial T2-weighted fluid-attenuated inversion recovery
4	Coronal 3D T1 gradient-recalled-echo
5	Sagittal T2-weighted
6	Magnetic resonance angiography (time-of-flight) of circle of Willis
7 (optional)	Proton magnetic resonance spectroscopy (1.5T) Magnetic resonance tractography (diffusion tensor imaging)

Table 3. Routine reporting template for mild cognitive impairment / dementia at the Prince of Wales Hospital, Hong Kong.

Presence of infarct(s) in cortex and subcortical nuclei
Presence of periventricular white matter change (focal or confluent)
Pattern of cortical atrophy (including hippocampus)
Ventricular and sulcal dilatation
Corpus callosum thickness at posterior genu
Magnetic resonance angiography of circle of Willis
Other findings
Magnetic resonance spectroscopy: N-acetyl aspartate/creatine ratio, myoinositol/creatine ratio

Table 4. Guide to interpretation of magnetic resonance spectroscopy findings at the Prince of Wales Hospital, Hong Kong.[9]

	N-acetyl aspartate/creatine ratio	Myoinositol/creatine ratio
Normal (Chinese data)	~1.3-1.5	0.65 ± 0.08
Physiological ageing	~1.2-1.3	0.65 ± 0.08
Mild cognitive impairment	Usually <1.2	Variable, but usually >0.7
Frontotemporal dementia or early Alzheimer's disease	1.1-1.2	~0.8-1.0
Established Alzheimer's disease	Usually <1.1	Usually near or >1.0

radiology reports.[10] Diagnostic accuracy for dementia can be improved when clinicians include relevant and specific clinical history in the referral forms.

In the following sections, we will discuss in detail the clinical and radiological features of non-AD dementias. The authors will discuss imaging findings of Lewy body dementia and normal-pressure hydrocephalus in the next article 'Neuroscintigraphy of non-Alzheimer's disease dementia' in this issue,[11] because the conventional imaging features of Lewy body dementia and normal-pressure hydrocephalus are often non-diagnostic and complimentary neuroscintigraphy can further improve the specificity.

FRONTOTEMPORAL DEMENTIA

FTD is a clinically heterogeneous group of non-AD dementias characterised by behavioural or cognitive deficits with early progressive personality, behaviour, or language changes. Patients affected by the disease tend to be younger than those with AD, with disease onset typically in the 50s or 60s. It is important to identify patients with FTD as they are usually young and FTD has a strong genetic component, with one-third of patients having an autosomal dominant inheritance pattern and an identifiable genetic mutation in 10% to 20%.[12] Early FTD can also be mistaken for primary psychiatric disorders, particularly if accompanied by psychotic features; imaging is crucial for demonstrating characteristic lobar atrophy patterns to support / refute the diagnosis. In addition, differentiation from AD is important in terms of management, as AD is responsive to cholinesterase inhibitors or memantine, whereas FTD is not responsive and these drugs may potentially aggravate behavioural symptoms. FTD is distinguished from AD by the absence of hippocampal atrophy in its early stage, despite the presence of dominant temporal lobe atrophy (Figure 1).

FTD is characterised by progressive atrophy of the frontal and anterior temporal lobes, with relative sparing of the posterior cortical areas in early stage (Figure 2), and is more often asymmetrical than symmetrical. FTD can be classified into behavioural-variant FTD, which is characterised by asymmetrical (often right-side predominant) frontal with or without temporal lobe atrophy, and language-variant FTD, which is characterised by asymmetrical (often left-side predominant) anterior temporal / inferior frontal lobe atrophy, and is closely related to the PPA group of dementias (due to its common pathogenesis of tauopathy). There is also significant clinical overlap between FTD, corticobasal degeneration (CBD), and PSP as the disease progresses.[13] Involvement of the orbitofrontal cortex has been reported as an early manifestation in FTD.[14]

In moderate-to-severe stages of FTD (Figure 3), there will inevitably be some degree of hippocampal atrophy, whereby the clinical and behavioural symptoms of FTD are quite marked and the clinical diagnosis of FTD should be obvious. Asymmetry has also been shown to be a distinctive feature of FTD, both in terms of its predilection for the frontal versus temporal lobes, and between the left and right hemispheres, whereas AD tends to be more symmetrical (Figure 3).[15]

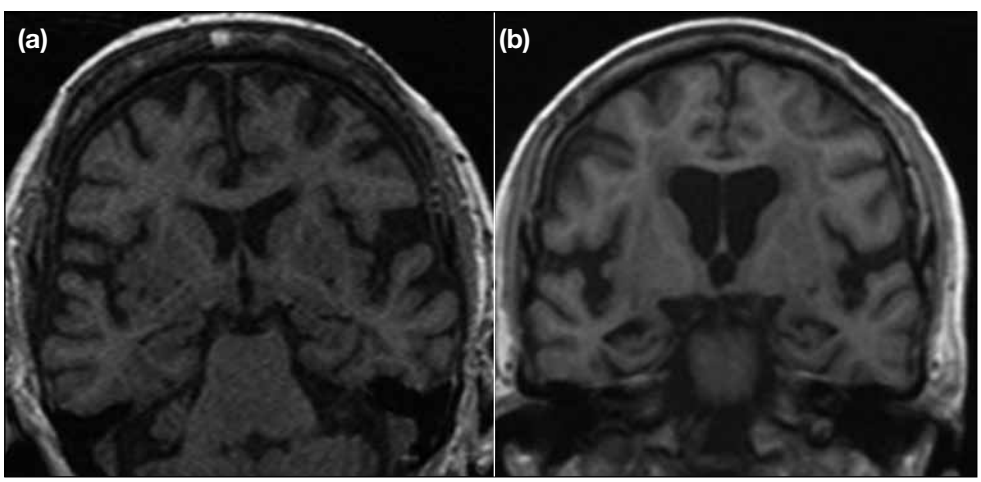


Figure 1. Magnetic resonance imaging: T1-weighted coronal images of (a) a patient with frontotemporal dementia showing asymmetrical mild-to-moderate left temporal atrophy, with unremarkable hippocampus, and (b) a patient with Alzheimer's disease showing symmetrical bilateral mild-to-moderate temporal and hippocampal atrophy.

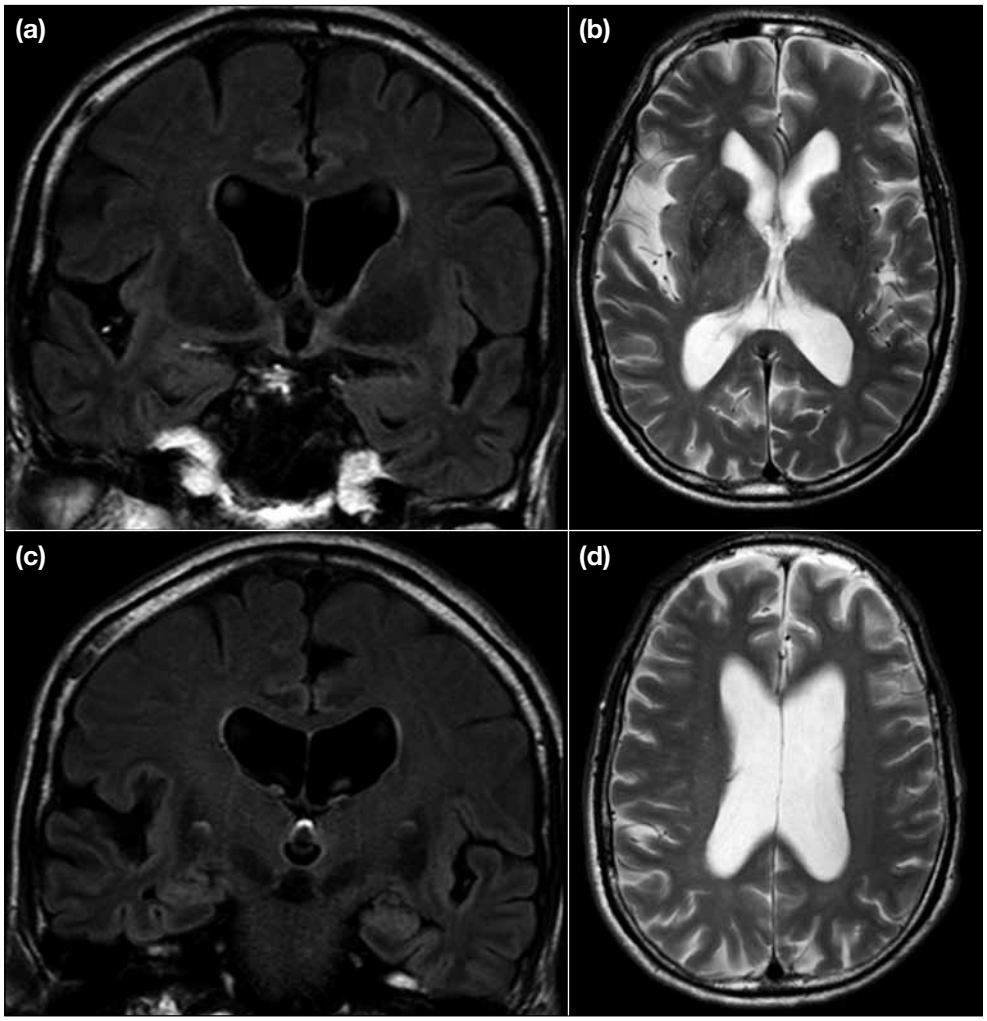


Figure 2. Magnetic resonance images of a patient with frontotemporal dementia. (a and c) Fluid-attenuated inversion recovery coronal images showing asymmetrical (R>L) mild-to-moderate temporal atrophy with unremarkable hippocampus, and (b and d) T2-weighted axial images showing mild frontoparietal atrophy, which is also common in early Alzheimer's disease or age-related atrophy.

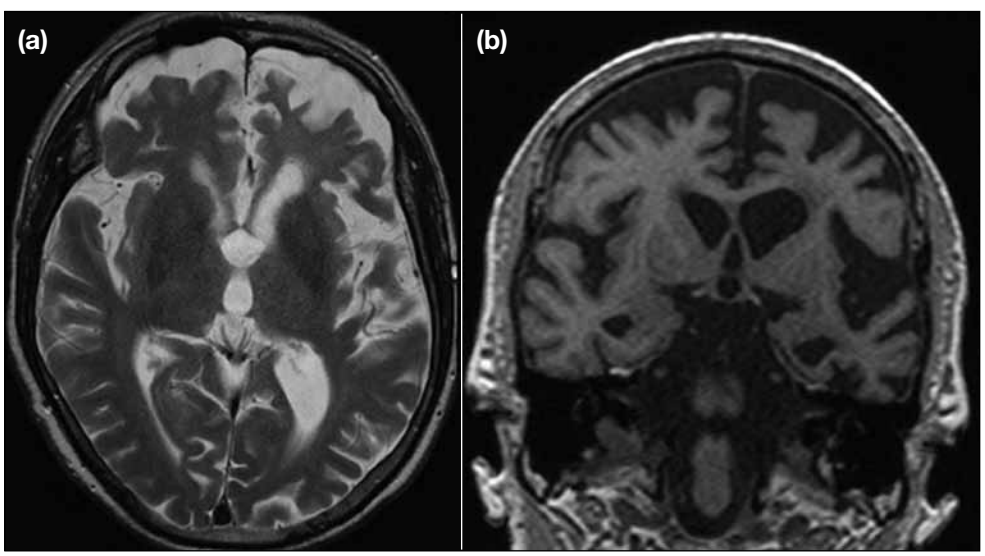


Figure 3. Magnetic resonance imaging: (a) axial T2-weighted and (b) and coronal T1-weighted images of a patient with severe frontotemporal dementia showing severe bilateral frontotemporal atrophy with moderate hippocampal atrophy. The distinct clinical features of the severe stage of frontotemporal dementia and dominant frontotemporal atrophy, rather than parietal atrophy, differentiate frontotemporal dementia from Alzheimer's disease despite coexisting hippocampal atrophy in severe frontotemporal dementia.

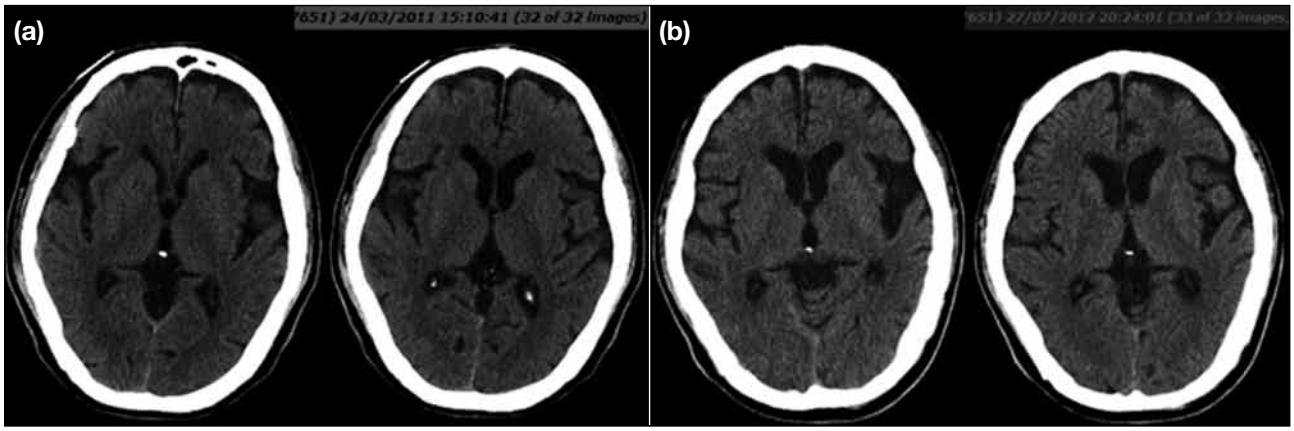


Figure 4. Computed tomography images of the brain of a 65-year-old man presenting with paucity in speech and apraxia. (a) Widening of the sylvian fissure is seen, and (b) 15 months later, widening of the progressive asymmetrical left sylvian fissure is seen, suggestive of perisylvian fissure atrophy. Clinically the patient was diagnosed with primary progressive aphasia.

Primary Progressive Aphasia

PPA is no longer considered to be a language variant of FTD and is viewed as a separate entity. The condition is characterised by prominent and isolated language deficit during the early phase, with gradual progressive impairment of language production, object naming, syntax, or word compression.[16] Other general and non-verbal cognitive functions are generally preserved or only affected later in the disease, thus distinguishing PPA from AD. There are three subtypes of PPA: (1) agrammatic variant (progressive non-fluent aphasia) characterised by agrammatism and apraxia of speech; (2) semantic variant characterised by impaired single-word comprehension and retrieval; and (3) logopenic variant characterised by impaired word finding and naming. Interestingly, the neuropathophysiology of PPA is extremely heterogeneous, with the agrammatic variant linked to tauopathy, the semantic variant linked to FTD-like ubiquitin-positive pathology, and the logopenic variant linked to AD-like pathology.

PPA is characterised by asymmetrical atrophy of the left side of the cerebral hemisphere (dominant hemisphere), which usually begins at the perisylvian region (Figure 4)[17] and gradually progresses to involve the entire left cerebral hemisphere, including the pericentral sulcus (Rolandic region) in the later stages. This can be radiologically indistinguishable from CBD in advanced disease, but the clinical presentation should be quite distinct because of the presence of speech-predominant symptoms in PPA versus motor-predominant symptoms in CBD.[18] There is also usually some degree of atrophy of the corpus callosum (Figure 5).

Different PPA subtypes have been reported to be associated with particular patterns of atrophy. The agrammatic / non-fluent variant is associated with atrophy of the left anterior perisylvian region, involving the posterior frontal, opercular, and insular regions. These are the areas of the brain that are also typically

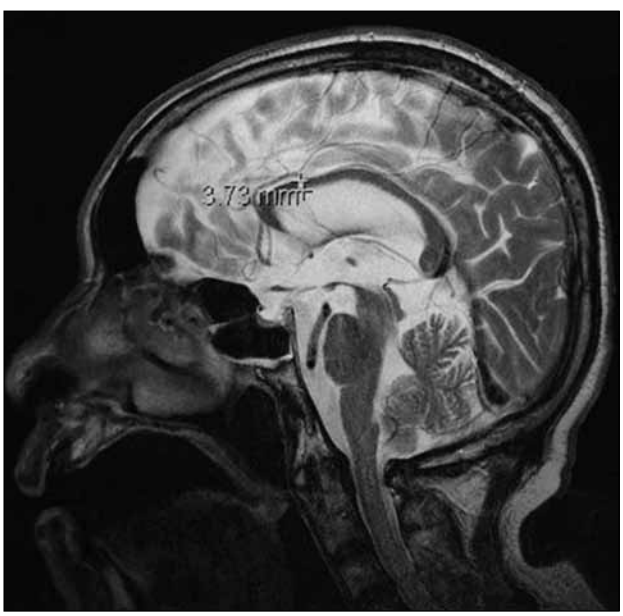


Figure 5. Magnetic resonance imaging: midline sagittal T2-weighted image of a patient with primary progressive aphasia showing thinning of the corpus callosum measured at the posterior part of the genu of the corpus callosum. Normal thickness is usually around 5 mm. There is also mild atrophy of the brainstem especially at the pons, with widening of the pre-pontine cistern and slender anterior border of the pons. Both features are commonly associated with advanced primary progressive aphasia.

implicated in Broca's aphasia (stroke-related language impediment), which is also characterised by effortful and dysfluent speech.[19] The semantic variant is associated with cortical atrophy of the ventral and lateral aspects of the anterior temporal lobes (more pronounced on the left side), together with the anterior hippocampus and amygdala. The logopenic variant is associated with atrophy of the left posterior perisylvian and inferior parietal regions.[20]

MR tractography can delineate the various white matter tracts for speech and hence demonstrate the respective fascicular atrophy involved in different PPA subtypes. The agrammatic / non-fluent variant is associated with atrophy of the arcuate fasciculus, which is the main speech conduction pathway between Broca's and Wernicke's areas. The logopenic variant is associated with atrophy of the frontoparietal fibres, which is an accessory speech conduction pathway.

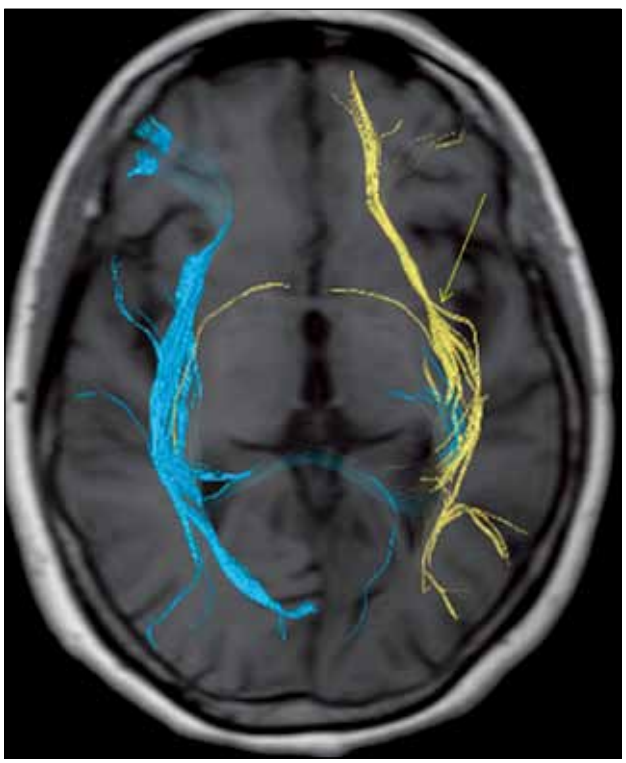


Figure 6. A magnetic resonance tractography image of the inferior longitudinal fasciculi (involved in speech production) of a patient with semantic variant of primary progressive aphasia. The left inferior longitudinal fasciculi (yellow) in the dominant hemisphere for speech production should be hypertrophic or equal to that of the non-dominant hemisphere in healthy patients. In this patient, the left inferior longitudinal fasciculi is atrophic compared with the right side.

The semantic variant is associated with atrophy of the uncinate fasciculus and inferior longitudinal fasciculus (Figure 6), which are both accessory speech pathways. However, this requires intense post-processing by dedicated personnel such as medical physicists, and is currently mainly reserved for research purposes (Figure 7).[21] Earlier characterisation of the exact subtype of PPA is also possible with perfusion studies (hexamethylpropyleneamine oxime or ^{99m}Technetium-ethylcysteinate dimer SPECT)[22] or metabolic brain scans (fluorodeoxyglucose positron emission tomography).

CORTICOBASAL DEGENERATION

CBD is characterised clinically by asymmetrical onset of limb rigidity, dystonia / myoclonus, postural instability, and localised cortical signs such as alien limb phenomenon and cortical sensory loss.

The radiological hallmark of CBD is asymmetrical frontoparietal cortical atrophy contralateral to the clinically affected side, which involves the pericentral sulcus (posterior frontal and superior parietal cortex) and gradually progresses to involve the perisylvian region in the later stages (Figure 8). There may be ex-vacuo dilatation of the lateral ventricle and asymmetric atrophy of the cerebral peduncle on the atrophic side.[23] Marked asymmetrical cerebral atrophy seen in late-

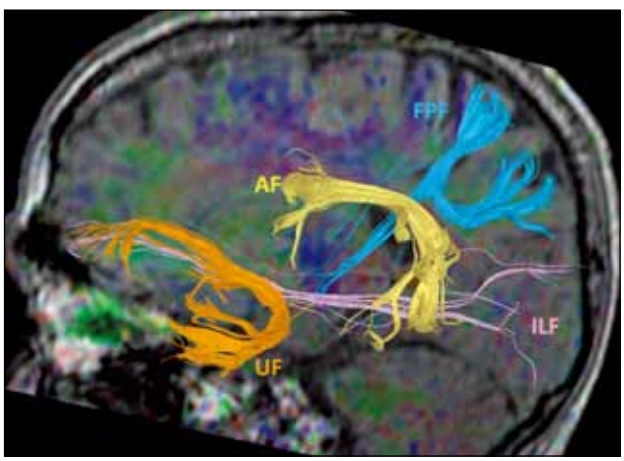


Figure 7. The fibre tracts involved in speech production shown in a magnetic resonance tractography image.
Yellow (arcuate fasciculus [AF]): the main conduction pathway for speech in agrammatic / non-fluent variant primary progressive aphasia; blue (frontoparietal fibres [FPF]): accessory speech conduction pathway in logopenic-variant primary progressive aphasia; orange (uncinate fasciculus [UF]) and pink (inferior longitudinal fasciculus [ILF]): accessory pathways in semantic-variant primary progressive aphasia.

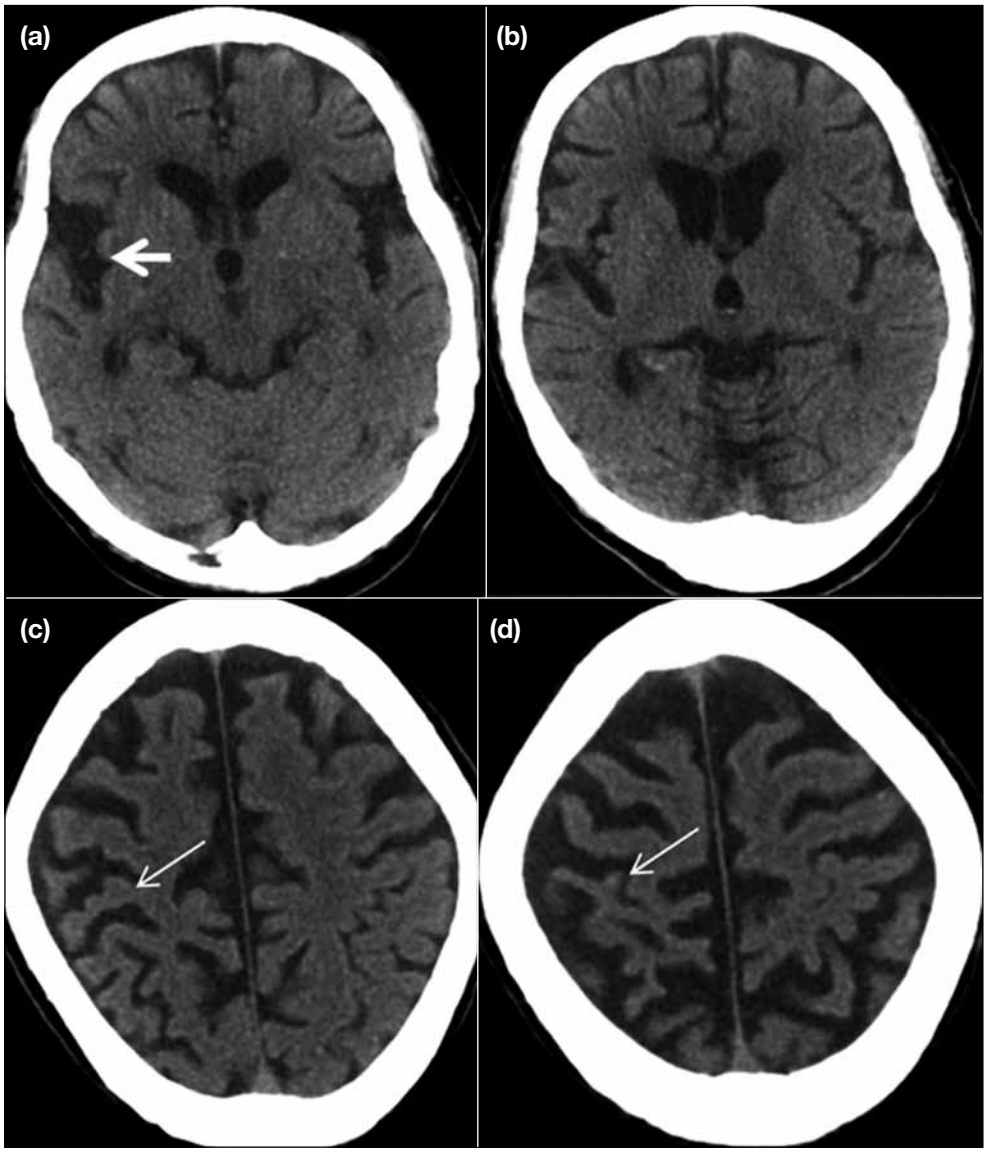


Figure 8. Computed tomography images of the brain of a patient with early-stage corticobasal degeneration showing (a and b) only subtle asymmetrical right perisylvian fissure atrophy (broad arrow), (c and d) right pericentral sulcus cerebral atrophy in the Rolandic region (narrow arrows). There is no evidence of a previous cerebrovascular accident to account for the cerebral atrophy.

stage CBD can be similar to FTD or PPA due to their common neuropathological basis of tauopathy, but the clinical features should be quite distinct (Figure 9).

Atrophy of the midbrain tegmentum is more commonly seen in late-stage disease and is best demonstrated on mid-sagittal images. Symmetrical T1-weighted high-signal intensity in bilateral subthalamic nuclei has also been reported in CBD.[24] Interestingly, the imaging abnormalities in the brainstem are also seen in patients in the early stage of progressive PSP. Distinguishing clinical features include symmetrical involvement and brainstem predominant symptoms in PSP (vertical gaze palsy), compared with asymmetrical involvement and cortical predominant symptoms in CBD (apraxia).

CBD is associated with subcortical white matter hyperintensity in the frontotemporal region on the atrophic side on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences. Pathologically, this corresponds with areas showing positive staining for anti-phosphorylated tau antibody on postmortem studies, hence confirming tauopathy as its neuropathology.[24] CBD is also associated with atrophy of the corpus callosum, particularly at its posterior middle portion.[25]

Newer directions in CBD research have shown increased median cerebral hemisphere apparent diffusion coefficient values in CBD patients compared with patients with Parkinson's disease and age-matched

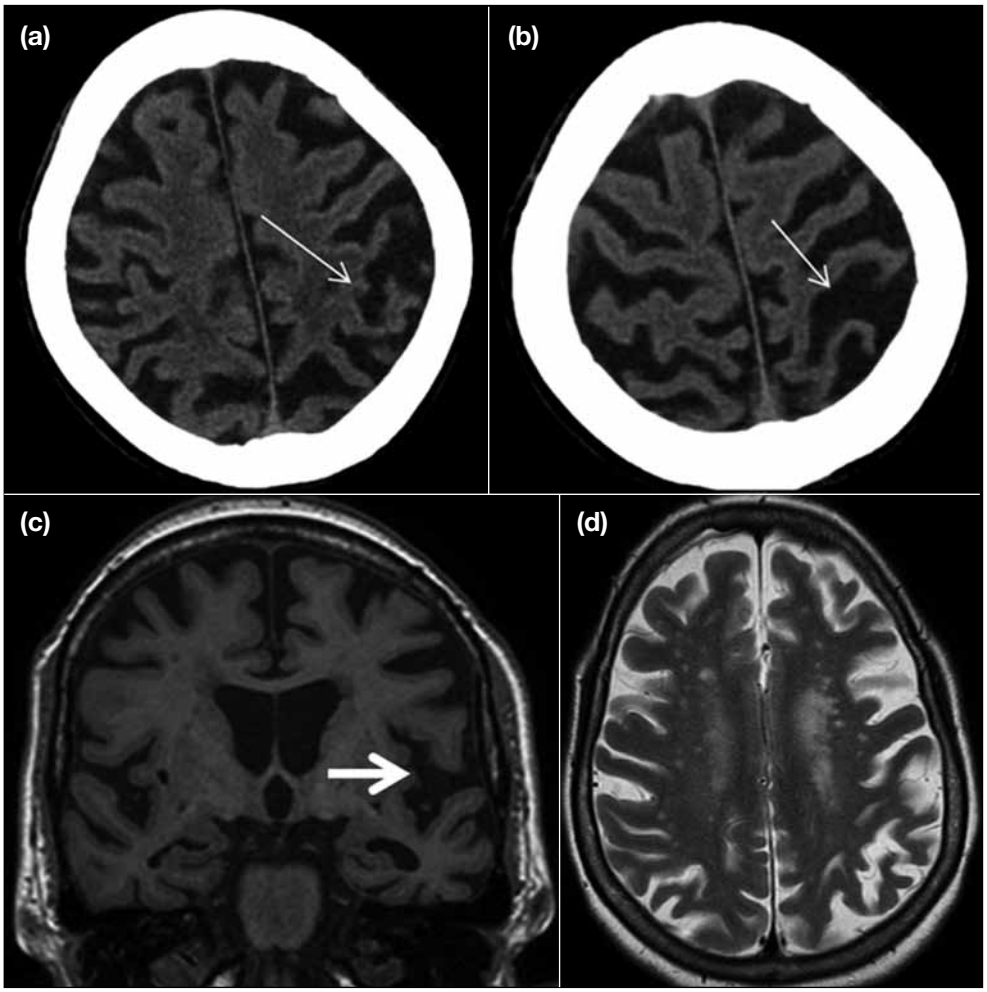


Figure 9. Computed tomography images of the brain showing (a and b) left pericentral sulcus cerebral atrophy in a patient with advanced stage corticobasal degeneration (narrow arrows). (c and d) Magnetic resonance images showing significant left frontotemporal atrophy, including the hippocampus, in the left perisylvian fissure region (broad arrow). The asymmetrical cerebral atrophy of advanced stage of corticobasal degeneration is similar to frontotemporal dementia or primary progressive aphasia due to common tauopathy, but their clinical features are distinct.

controls on diffusion-weighted imaging.[26] SPECT will demonstrate characteristic hypoperfusion of the contralateral frontoparietal cerebral cortex and basal ganglia in CBD,[23] which distinguishes it from PPA, in which there is normal basal ganglia uptake.

PROGRESSIVE SUPRANUCLEAR PALSY

PSP is considered a Parkinson plus syndrome, which is characterised clinically by vertical gaze palsy, postural instability and falls, parkinsonian features, pseudobulbar palsy, and cognitive impairment. Clinical differentiation of PSP from Parkinson's disease and multiple system atrophy of the Parkinson type (MSA-P) may be difficult in early disease.

The neuropathological characteristics of PSP are neuronal degeneration and loss in the midbrain tegmentum, atrophy of the substantia nigra, and changes in the red nucleus and globus pallidus.[27] Radiologically, this is mirrored by early atrophy of the midbrain and superior cerebellar peduncles, resulting in progressive flattening and excavation of the superior profile of the midbrain,[28] which culminates in the classical hallmark penguin silhouette sign / hummingbird sign (atrophy of the midbrain tegmentum with relative preservation of the pons) seen on mid-sagittal images. There is usually commensurate dilatation of the third ventricle and cerebral aqueduct as a result of the midbrain atrophy. Pontine atrophy is usually featured later in the disease course, resulting in widening of the prepontine cistern and slender anterior border of the pons (Figure 10). Conversely, in MSA-P, there is disproportionate atrophy of the pons instead of the midbrain; hence the ratio of the area of the midbrain to the area of the pons on mid-sagittal images has been shown to reliably differentiate between PSP and MSA-P in several studies.[29,30]

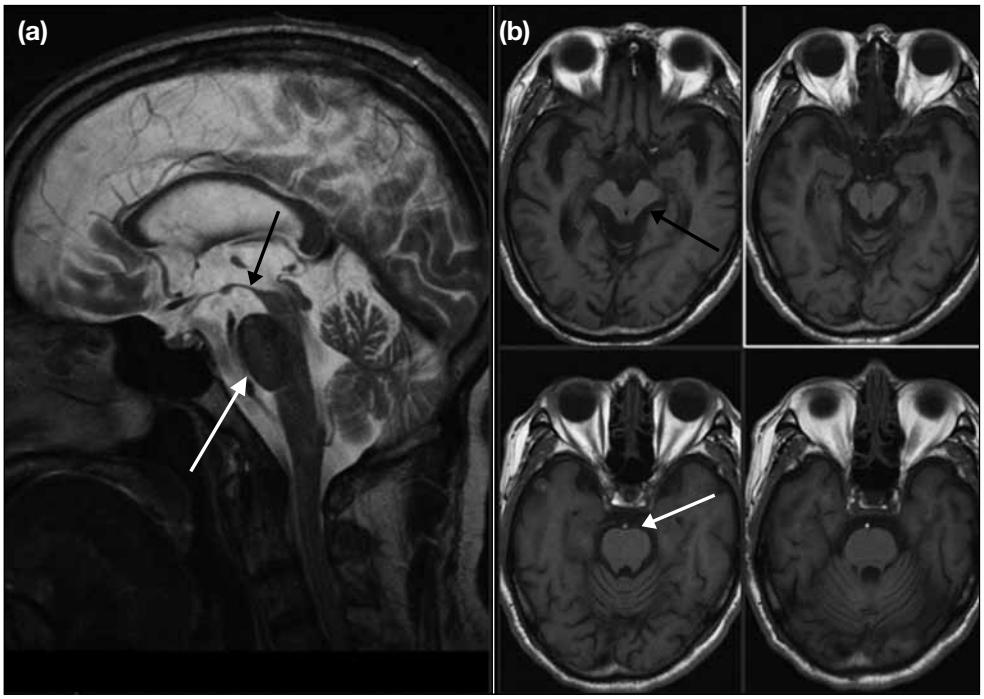


Figure 10. Magnetic resonance images of a patient with progressive supranuclear palsy. (a) A sagittal T2-weighted image showing a widened prepontine space and mild pontine atrophy (white arrow) and moderate midbrain tegmentum atrophy giving rise to Hummingbird sign (black arrow), and (b) axial T1-weighted images showing moderate midbrain atrophy over the cerebral peduncles (black arrow) and mild pontine atrophy (white arrow).

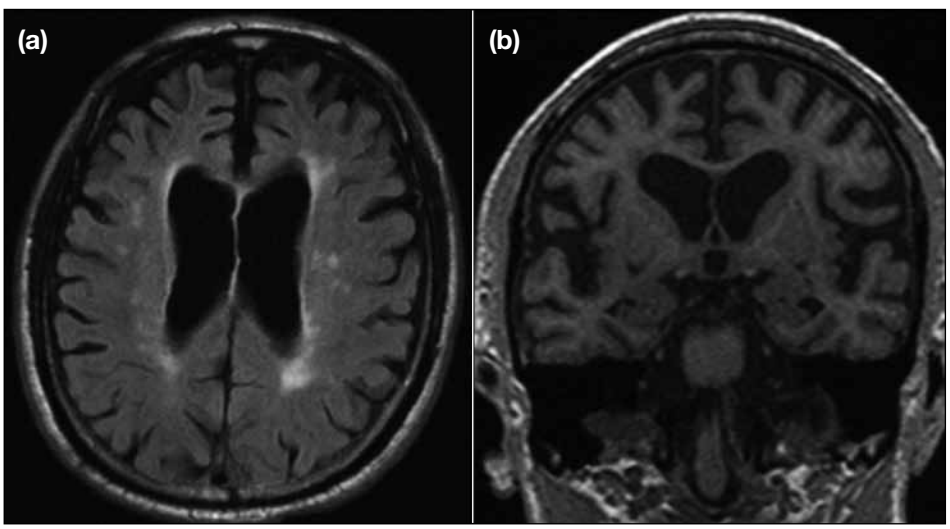


Figure 11. Magnetic resonance images of the patient with progressive supranuclear palsy in **Figure 10**. (a) Axial fluid-attenuated inversion recovery showing mild and non-confluent periventricular hyperintense changes not significant for small vessel disease. Bilateral symmetrical mild frontal atrophy is present. (b) A coronal T1-weighted image showing slightly asymmetrical perisylvian atrophy (more on the right side) with unremarkable hippocampus. Supratentorial atrophy in progressive supranuclear palsy is similar to frontotemporal dementia due to common tauopathy, but is not compatible with Alzheimer's disease.

There may also be abnormal T2 periaqueductal hyperintensity in the midbrain tegmentum, which has been shown to correspond with neuronal degeneration in this region on neuropathological studies,[31] although this is a specific, but infrequently demonstrated, sign. PSP is also associated with non-specific atrophy of the thalamus and striatum and mild atrophy of the frontal lobes. Supratentorial cortical atrophy is relatively minor in PSP, which makes it a distinguishing feature from CBD[32] but, when present, it is usually asymmetrical and similar to the FTD pattern due to its common tauopathy origin (Figure 11). Cerebellar atrophy is usually absent in PSP, which distinguishes it from MSA.

The definitive diagnosis of PSP may be difficult in the early stages of the disease when midbrain atrophy may be subtle on morphological studies. In such cases, SPECT or positron emission tomography may aid diagnosis by demonstrating disproportional brainstem hypoactivity.

MULTIPLE SYSTEM ATROPHY

MSA is characterised by a combination of parkinsonism, cerebellar dysfunction, and autonomic disturbance, which result from overlapping pathologies, including striatonigral, olivopontocerebellar, and central autonomic degeneration. MSA is divided into two clinical phenotypes, depending on the initial and predominant symptom. The more frequent phenotype is MSA-P, which presents with predominantly parkinsonian features and few, if any, cerebellar signs (also known as striatonigral degeneration). The other phenotype is MSA-C, which presents with predominantly cerebellar dysfunction (also known as olivopontocerebellar atrophy).[33] Clinical differentiation between Parkinson's disease, MSA-P, and PSP may be difficult in the early stages of the disease.

MSA is characterised by progressive atrophy of infratentorial structures, classically involving the cerebellum, middle cerebellar peduncles, pons, and midbrain (Figure 12). There may be associated T2-hyperintense signal changes in the pontocerebellar tract. The classical 'hot cross bun' sign describes the pattern of cruciform T2 hyperintensity in the pons (Figure 13), which is due to selective loss of transverse pontocerebellar fibres and pontine raphe neurons with preservation of the pontine tegmentum and corticospinal tracts. Brainstem abnormalities are more prominent in patients with MSA-P, while cerebellar abnormalities are more prominent in MSA-C, although there is a wide range of imaging overlap between the two subtypes.[34] Conversely, patients with Parkinson's disease seldom develop brainstem atrophy.

In addition, supratentorial abnormalities, including putaminal atrophy, hypointensity of the putaminal body, and slit-like hyperintensity of the putaminal posterolateral margin, have been reported in MSA-P. The neuropathological basis for these findings is reversal of the normal iron distribution with increased iron deposition in the putamen, resulting in severe putaminal hypointensity relative to the globus pallidus. This is contrary to Parkinson's disease, where there is normal iron distribution, for example globus pallidus hypointensity relative to the putamen.[35] The degree of putaminal atrophy has been found to correlate with the severity of extrapyramidal signs in MSA-P.[36]

There may also be atrophy of the supratentorial cerebral hemispheres, especially in the frontal and parietal lobes, but this is usually mild and should not be significantly progressive over time,[34] in contrast to the progressive infratentorial atrophy that is the hallmark of this condition.

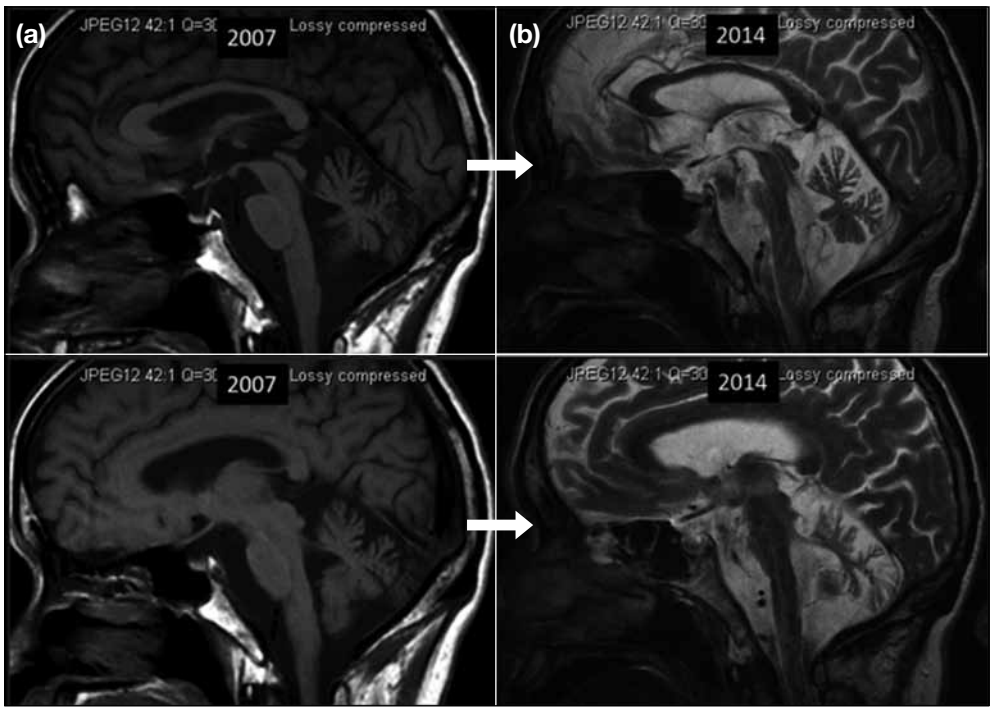


Figure 12. Sagittal magnetic resonance images of the infratentorial region of a patient with multiple system atrophy showing progressive olivopontocerebellar atrophy over 7 years from 2007 (left-sided panels) to 2014 (right-sided panels). The pontine atrophy is more severe than midbrain atrophy in multiple system atrophy. There is insignificant supratentorial progressive atrophy.

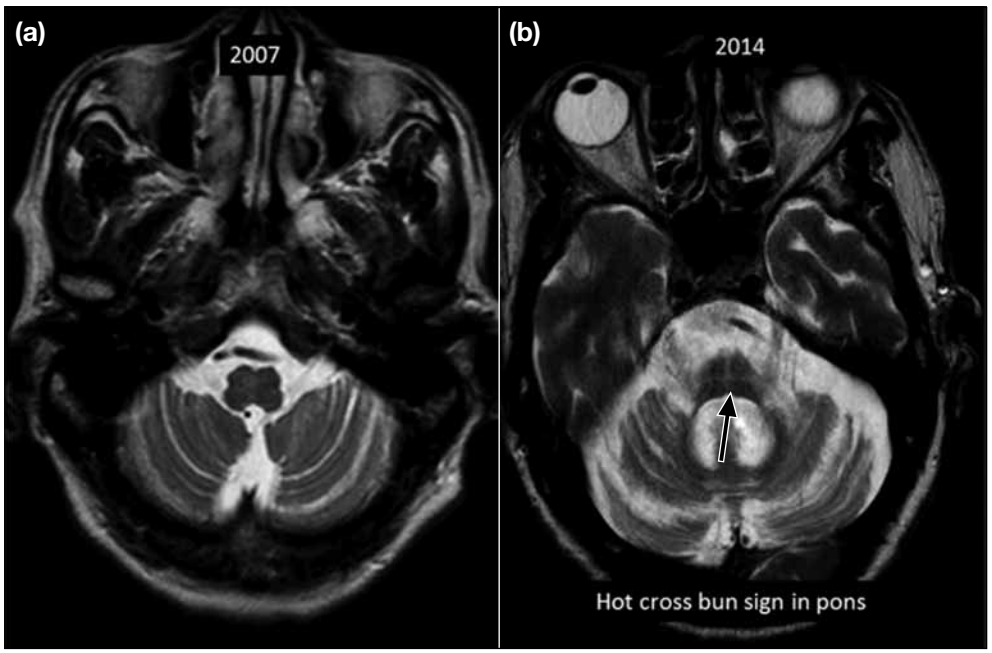


Figure 13. Magnetic resonance imaging: axial T2-weighted images of the pontocerebellar region of the patient with multiple system atrophy in **Figure 12**. There is progressive pontine atrophy over 7 years in (a) 2007 and (b) 2014. The typical 'hot cross bun' sign is seen in the pons (arrow). This patient has the multiple system atrophy with cerebellar dysfunction subtype, with predominant cerebellar signs clinically.

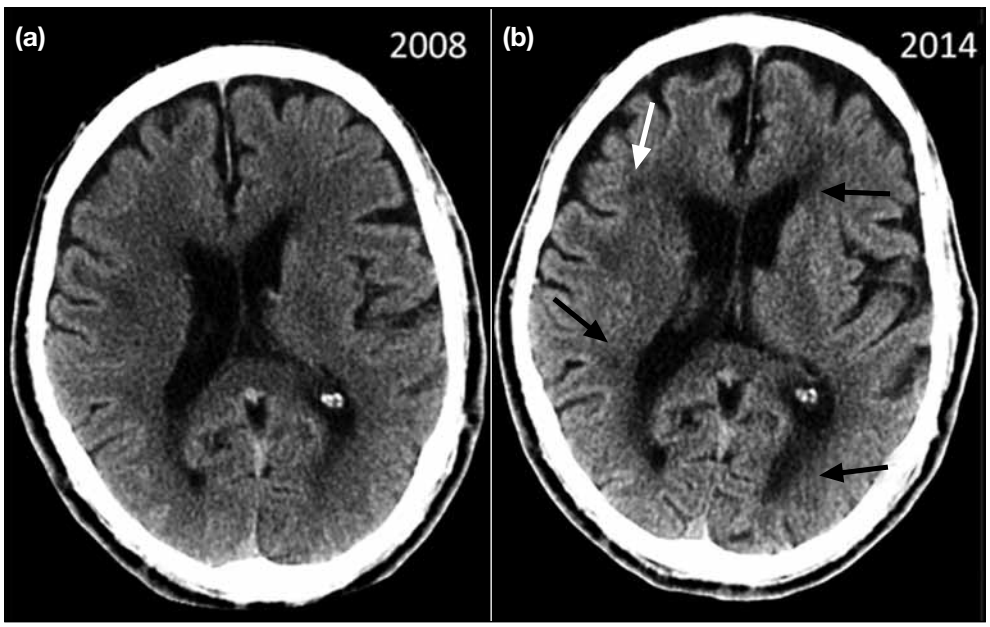


Figure 14. Computed tomography of the brain of an elderly man with hypertension showing progressive periventricular hypodensities over 6 years in (a) 2008 and (b) 2014. The latest image (b) shows a small subcortical infarct (white arrow) and early confluent changes (black arrows) of periventricular leukoencephalopathy representing early small vessel disease. There is also mild progressive cerebral atrophy with sulcal widening.

VASCULAR DEMENTIA

VaD is the second most common cause of dementia after AD, with the incidence increasing with age. VaD is associated with cardiovascular risk factors such as chronic hypertension and atherosclerosis. The presenting clinical symptoms and signs are highly variable depending on the anatomical areas affected. The clinical course may be stepwise in patients with periodic accumulation of large vessel or strategic infarcts, but is more commonly slowly progressive in patients with small vessel disease.

The NINDS-AIREN criteria for VaD are a set of diagnostic standards encompassing clinical, radiological, and neuropathological features for the diagnosis of VaD that are widely used in research studies. The

NINDS-AIREN criteria classify patients as having possible, probable, or definite VaD. The radiological features included in the criteria are multiple large vessel infarcts, a single strategically placed infarct, multiple basal ganglia and white matter lacunes, extensive periventricular white matter lesions, or a combination, and these are graded by topography and severity.[3]

Small vessel disease is an important predictor of cognitive decline and may amplify the pathological changes in AD. Small vessel disease may result in cognitive decline if there are multiple (>2) lacunar infarcts in the frontal white matter and basal ganglia, bilateral thalamic infarcts, and extensive periventricular white matter lesions (>25% of total white matter). Periventricular white matter lesions present initially as multiple punctate lesions that gradually coalesce to form diffuse confluent periventricular signal abnormalities, which are hypodense on CT, and T2 and FLAIR hyperintense on MRI (Figures 14 and 15). MRI is preferred over CT as it is more sensitive for detecting small vessel disease.[37] In the late stages of VaD, there may be global cerebral atrophy and compensatory ventricular dilatation commensurate with the degree of atrophy.

PSEUDODEMENTIA

Pseudodementia is a psychiatric condition that usually occurs in patients with major depression and bipolar affective disorder, whereby patients present with dementia-like symptoms such as cognitive impairment, apathy, and irritability. Pseudodementia is frequently

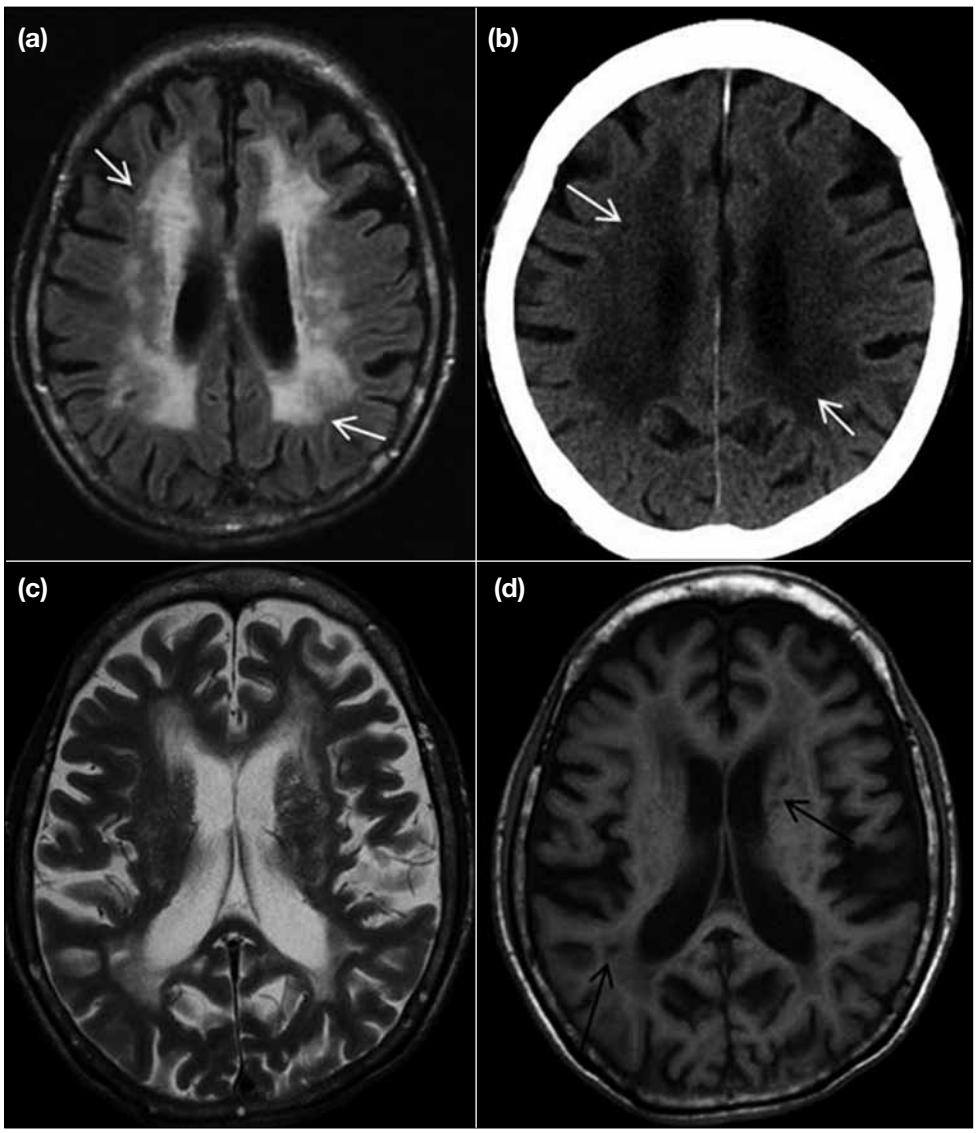


Figure 15. (a) Magnetic resonance fluid-attenuated inversion recovery and (b) computed tomography images of severe small vessel disease with confluent periventricular changes (white arrows). (c) T2-weighted and (d) T1-weighted magnetic resonance images showing multiple infarcts in the corona radiata and subcortical region (black arrows).

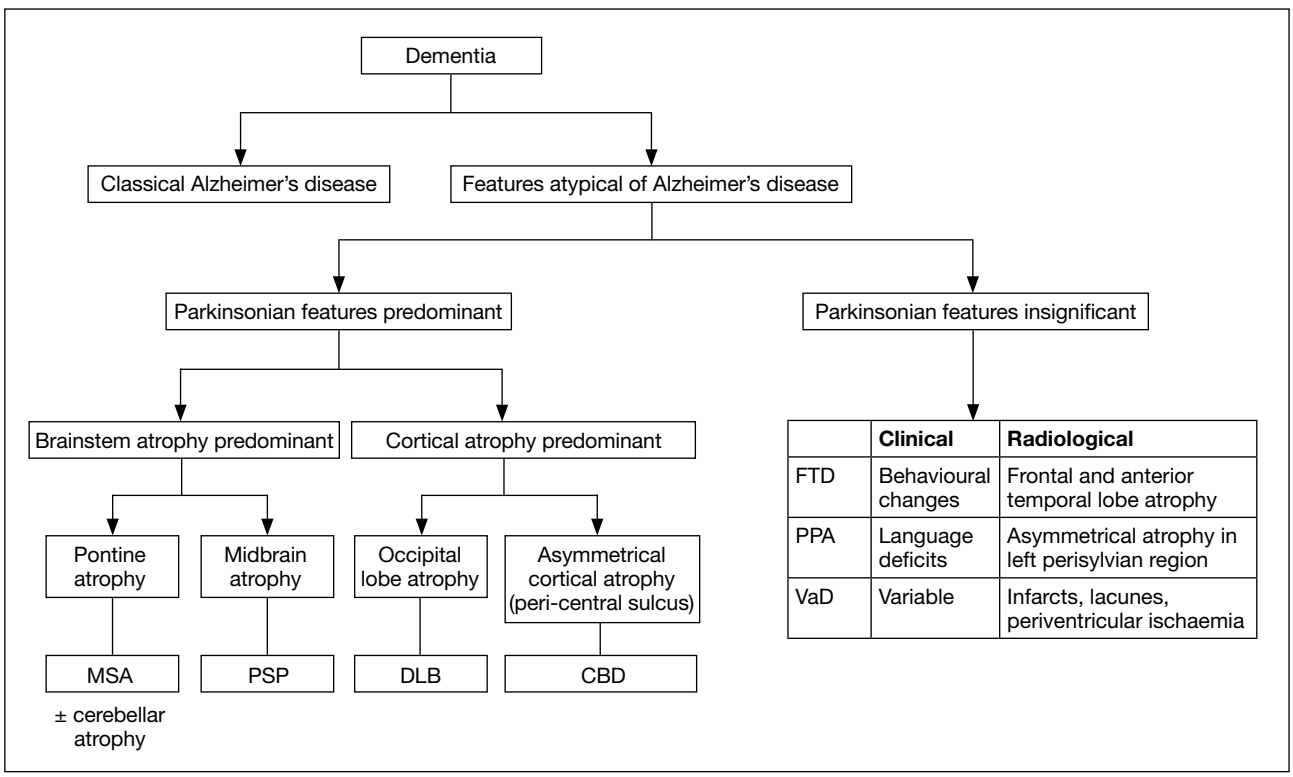
confused with FTD when affected patients are in their 50s or 60s. Neuroimaging, particularly MRI, is helpful to exclude organic causes of dementia. The authors' experience is that these psychiatric patients typically have normal MRS values and no or minimal atrophy on MRI at early presentation, which is concordant with a previous study demonstrating minimal hippocampal atrophy in patients with pseudodementia.[38]

DISCUSSION

The pattern of cerebral atrophy in dementia is specific if reviewed in a systematic manner. When combined with advanced MRI techniques such as MRS to detect earlier metabolic derangements in neurometabolites and, occasionally, diffusion tensor imaging (tractography) to delineate atrophic fibre tracts, we can often arrive at a specific diagnosis or a narrow list of differential diagnoses. Correlation with the clinician's provisional diagnosis and comparison with previous imaging or follow-up scans usually help to resolve the clinical challenge of diagnosing dementia. The authors advocate detailed review of clinical records, systematic analysis of anatomical structures, and discussion with the referring clinicians as being essential for formulating a specific radiological opinion. Further evaluation may sometimes require neuroscintigraphy such as SPECT or functional MRI for biochemical and functional analysis, although these techniques are not always readily accessible and are often reserved as second-line investigations. A summary flowchart for diagnosis of non-AD dementia is shown in Figure 16.

CONCLUSION

Routine systematic review of cerebral atrophy patterns and background knowledge of the vast clinical spectrum of dementias, in conjunction with the use of advanced MRI and neuroscintigraphy in selected cases, will often aid radiologists in deriving appropriate differential diagnoses of different dementias. Although MRI is much better for analysis of anatomical detail in brain, it is the authors' experience that the atrophic patterns of dementias can also be reviewed in multiplanar CT imaging, which is usually the first neuroimaging method for dementia patients. However, if neuroradiology



	Clinical	Radiological
FTD	Behavioural changes	Frontal and anterior temporal lobe atrophy
PPA	Language deficits	Asymmetrical atrophy in left perisylvian region
VaD	Variable	Infarcts, lacunes, periventricular ischaemia

Figure 16. Summary flowchart for diagnosis of non-Alzheimer's disease dementias with predominant and insignificant parkinsonian features.

Abbreviations: CBD = corticobasal degeneration; DLB = Lewy body dementia; FTD = frontotemporal dementia; MSA = multiple system atrophy; PPA = primary progressive aphasia; PSP = progressive supranuclear palsy; VaD = vascular dementia.

imaging is not sufficient to arrive at a suggestive diagnosis, further neurofunctional scintigraphy has to be considered. This will be discussed in the next article 'Neuroscintigraphy of non-Alzheimer's disease dementia' in this issue.[11]

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