PRACTICE

RATIONAL IMAGING

Suspected early dementia

This article explores how imaging can be used to investigate a patient with suspected early dementia

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This series provides an update on the best use of different imaging methods for common or important clinical presentations. The series advisers are Fergus Gleeson, consultant radiologist, Churchill Hospital, Oxford, and Kamini Patel, consultant radiologist, Homerton University Hospital, London. To suggest a topic for this series, please email us at practice@bmj.com.

A 58 year old right handed woman was referred with a three year history of word finding difficulty and poor memory. Problems with reading, calculation, and spelling had emerged more recently. She could find her way around and was still driving. She was more irritable and less outgoing. Her symptoms were slowly progressive with a suggestion of day to day variability. There was no significant past medical history and she took no medications. There was a family history of cardiovascular disease but not of dementia. She did not drink alcohol to excess but had a 25 pack year smoking history. The physical examination was unremarkable. The mini mental state examination score was 25/30: she could recall all three items after a delay, but lost points on orientation, naming, calculation, and for following a three stage command. Initial investigations, including full blood count, electrolytes, liver function, thyroid function, erythrocyte sedimentation rate, vitamin B12, folate, and a chest x ray, were normal.

What is the differential diagnosis?

As with many patients presenting with early cognitive problems, the differential diagnosis is wide. Anxiety and depression are associated with cognitive symptoms and they also complicate established dementia. Space occupying lesions including tumours, though unlikely, require consideration. Dementia—acquired, progressive cognitive impairment sufficient to impair activities of daily living—is more typically encountered in older people, but is not uncommon at younger ages.¹ In an ex-smoker with a family history of cardiovascular disease, vascular cognitive impairment, which can be associated

with focal cognitive symptoms, depression, and insidious rather than stepwise cognitive decline, should be considered.

Alzheimer's disease is the most common neurodegenerative cause of dementia. The history of memory and executive decline in the context of fluctuations makes dementia with Lewy bodies possible, even without parkinsonism or visual hallucinations. Naming and behavioural problems are commonly seen within the frontotemporal lobar degeneration spectrum, which includes behavioural variant frontotemporal dementia (previously Pick's disease), progressive non-fluent aphasia, and semantic dementia (fluent speech with loss of word meaning).

Critically, distinguishing these causes from one another has implications for management, as acknowledged in UK national dementia guidelines.² Surgery for an intracranial mass lesion is potentially curative, as is pharmacotherapy for depression. Even in the absence of disease modifying therapies, other dementia disorders still require specific treatment strategies, such as modification of vascular risk factors in vascular cognitive impairment, and acetylcholinesterase inhibition for Alzheimer's disease and dementia with Lewy bodies, for example. Accurate diagnosis facilitates prognosis and counselling, referral to appropriate services and voluntary organisations, applications for relevant benefits, and important lifestyle, occupational, and legal decisions, including those related to driving.

How can brain imaging help?

Although a detailed clinical assessment remains the mainstay of the evaluation of a patient with early dementia, UK, European, and US guidelines recommend that all patients with cognitive impairment should undergo structural imaging as part of the diagnostic work up.^{3 4 5} Brain imaging is increasingly used to help distinguish different forms of dementia from one another, whereas in the past it was principally undertaken to exclude treatable intracranial mass lesions, haematomata, and

Learning points

- All patients with suspected dementia should have structural brain imaging
- Structural imaging is useful not only for excluding intracranial space occupying lesions, but also for arriving at a specific dementia subtype diagnosis
- The pattern of regional brain atrophy—particularly using high resolution volumetric magnetic resonance imaging (MRI)—has value in distinguishing the common neurodegenerative causes of dementia
- T2 weighted and fluid attenuated inversion recovery (FLAIR) MRI sequences are highly sensitive to ischaemic damage in the cerebral white matter
- Other MRI sequences and imaging modalities (including positron emission tomography (PET) and dopamine transporter (DAT) scans) have diagnostic value in particular clinical settings.

hydrocephalus, which account for less than 1% of all cases of dementia.³

Computed tomography

Where magnetic resonance imaging (MRI) is not available or contraindicated, computed tomography (which does involve exposure to ionising radiation) can usefully exclude major space occupying lesions, hydrocephalus, and large infarcts. Modern multidetector computed tomography scanners make it possible to acquire volumetric imaging data of the whole brain in a few seconds, which allows high resolution multiplanar reconstructions to be performed. Images reconstructed in the coronal plane allow detailed assessment of the medial temporal lobe structures (fig 1).

Magnetic resonance imaging

MRI, with its superior contrast resolution, is increasingly preferred over computed tomography in the evaluation of suspected dementia.² A basic dementia sequence including a high resolution structural volumetric T1 weighted scan and T2 weighted or fluid attenuated inversion recovery (FLAIR) sequences can be obtained in approximately 20 minutes. MRI does not involve ionising radiation, but claustrophobia may be a limiting factor in some patients. MRI is contraindicated in patients with pacemakers and certain metallic implants, and earplugs should be worn to prevent the possibility of cochlear damage.

T1 weighted volumetric MRI scanning provides a very detailed assessment of brain structure, allowing for the assessment of the presence or absence and pattern of brain volume loss, ie, atrophy. When evaluating a patient with cognitive impairment it is particularly valuable to assess for medial temporal lobe atrophy on coronal reformats, either qualitatively or using simple rating scales. The presence of bilateral, symmetrical hippocampal atrophy distinguishes mild Alzheimer's disease from controls with approximately 80-85% sensitivity and specificity (fig 2A).⁴⁻⁶ Alzheimer's disease is also associated with relatively greater and more disproportionate hippocampal atrophy than dementia with Lewy bodies (fig 2B).⁷ In contrast, asymmetric temporal lobe atrophy with an anterior>posterior gradient is at least 85% specific for frontotemporal lobar degeneration,⁸ and focal left inferior/anterior temporal lobe atrophy is highly suggestive of semantic dementia (fig 2C).⁹ The presence of medial temporal lobe atrophy in patients with isolated memory impairment (mild cognitive impairment) has high predictive value for the subsequent development of Alzheimer's disease,¹⁰ and this has been incorporated into new proposed diagnostic criteria.¹¹⁻¹² However, the absence of medial temporal lobe atrophy does not exclude a diagnosis of Alzheimer's disease, and patients with young onset Alzheimer's

disease may have prominent posterior atrophy with relative sparing of medial temporal lobe structures.

T2 weighted or FLAIR sequences are highly sensitive for detecting white matter abnormalities, which can reflect demyelination but, much more commonly in this age group, cerebrovascular disease. As well as detecting major strokes, these sequences allow visualisation of small strategic infarcts (such as within the thalamus and other subcortical nuclei) and small vessel ischaemic white matter damage. Although an increased white matter lesion load suggests vascular disease, particularly in combination with lesions in the basal ganglia and brain stem, the pathophysiology and cognitive consequences of MRI white matter hyperintensities remain the subject of ongoing research,¹³ and it is important not to over interpret minor vascular disease that commonly accompanies ageing. Significant white matter and other ischaemic changes in the presence of hippocampal atrophy support a diagnosis of mixed vascular cognitive impairment/Alzheimer's dementia (fig 2D).

MRI scanning using a variety of additional sequences can provide other valuable diagnostic information. Thus, in the correct clinical context, the presence of temporal lobe signal change is suggestive of infection or inflammation (fig 3A);¹⁴ diffusion weighted imaging can help distinguish acute from chronic vascular disease, and the finding of neocortical or striatal abnormalities can aid the diagnosis of Creutzfeldt-Jakob disease (fig 3B);¹⁵ and T2* sequences sensitive to iron deposition can demonstrate microhaemorrhages due to amyloid angiopathy (fig 3C) or vascular disease.¹⁶

Metabolic and functional imaging

Although metabolic or functional imaging is typically not performed routinely, it can provide valuable diagnostic information in certain circumstances. Where dementia with Lewy bodies is suspected, demonstration of central dopamine depletion using positron emission tomography (PET) (fig 4A) or single photon emission computed tomography (SPECT) dopamine transporter (DAT) scanning has good diagnostic sensitivity and specificity (78% and 90% in one study¹⁷), and is now included as a suggestive feature in diagnostic criteria.¹⁸ The demonstration of temporoparietal hypometabolism using fluorodeoxyglucose (FDG) PET or SPECT scanning supports a diagnosis of Alzheimer's disease over frontotemporal lobar degeneration (fig 4B);¹⁹ and in patients with personality or behavioural change in whom structural scanning is normal, the demonstration of focal frontal hypometabolism using FDG-PET scanning supports a diagnosis of frontotemporal lobar degeneration.²⁰ Currently research tools, new PET tracers appear to have very high sensitivity and specificity for detecting cerebral amyloid pathology (Fig 4C, D), and are likely to find clinical utility in the near future.²¹ All these techniques involve

the injection of radioactive tracers, with a small exposure to ionising radiation.

Outcome

Our patient underwent MRI, which revealed no evidence of a space occupying lesion, and very minor vascular load. There was highly asymmetric left temporal lobe atrophy with an anterior>posterior gradient (fig 2C). Neuropsychometric testing confirmed profound anomia and semantic memory impairment. A diagnosis of frontotemporal lobar degeneration, semantic dementia variant was made. Treatment with acetylcholinesterase inhibition was not indicated;² the patient contacted the driving authorities and stopped driving; and was referred for speech and language therapy and to the Pick's Disease Support Group.

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Patient consent obtained.

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Further reading

- *Neuroimaging in dementia*. Barkhof F, Fox NC, Bastos-Leite AJ, Scheltens P, eds. Springer-Verlag, 2011

Figures

Fig 1 Bilateral medial temporal lobe atrophy (right hippocampus illustrated with arrows) in the same subject with Alzheimer's disease demonstrated on coronal images acquired with: (A) 64 detector row computed tomography scanning; (B) 1.5 tesla MRI volumetric T1 weighted sequence (adapted from Wattjes MP, Henneman WJ, van der Flier WM, de Vries O, Träber F, Geurts JJ, et al. Diagnostic imaging of patients in a memory clinic: comparison of MR imaging and 64-detector row CT. *Radiology* 2009;253:174-83, with permission)

Fig 2 (A) T1 weighted coronal volumetric MRI at 1.5 tesla showing symmetrical medial temporal lobe (MTL) atrophy (circled) in postmortem proven Alzheimer's disease; (B) T1 weighted coronal volumetric MRI at 1.5 tesla showing relative sparing of MTL structures (circled) in postmortem proven dementia with Lewy bodies; (C) T1 weighted coronal volumetric MRI at 3 tesla showing highly asymmetric inferior left temporal lobe and hippocampal atrophy (arrows) in frontotemporal lobar degeneration, semantic dementia subtype; (D) T2 weighted coronal volumetric MRI at 1.5 tesla showing symmetrical MTL atrophy (circled) and small vessel white matter disease (arrows) in a patient with clinically diagnosed mixed vascular/Alzheimer's disease (D: adapted from Bastos Leite AJ, Scheltens P, Barkhof F. Pathological aging of the brain: an overview. *Top Magn Reson Imaging* 2004;15:369-89, with permission)

Fig 3 (A) Axial FLAIR MRI showing left hippocampal swelling and hyperintensity (arrow) in voltage gated potassium channel complex antibody associated limbic encephalitis; (B) Axial diffusion weighted MRI in a patient with sporadic Creutzfeldt-Jakob disease demonstrating widespread areas of confluent bilateral cortical restricted diffusion with similar restricted diffusion in the caudate nuclei and left putamen; (C) axial gradient—echo T2* weighted imaging demonstrates multiple microbleeds (examples circled) indicating cerebral amyloid angiopathy in a patient with familial Alzheimer's disease (A: adapted from Barkhof F, Fox NC, Bastos-Leite AJ, Scheltens P, eds. *Neuroimaging in dementia*. Springer-Verlag, 2011, with permission; B: image courtesy Harpreet Hyare, MRC Prion Unit, University College London; C: adapted from Ryan NS, Bastos-Leite AJ, Rohrer JD, Werring DJ, Fox NC, Rossor MN, et al. Cerebral microbleeds in familial Alzheimer's disease. *Brain* 2011; Jun 17, with permission)

Fig 4 (A) Dopamine transporter imaging shows symmetrical reduced basal ganglia uptake (dot-like, rather than comma-like, in appearance) in a patient with clinically probable dementia with Lewy bodies; (B) FDG-PET shows right frontotemporal hypometabolism (arrow) in a patient with clinically probable behavioural variant frontotemporal dementia. Warm colours represent high glucose uptake; (C, D) F18 (florbetapir) amyloid PET imaging shows absence of significant binding in (C) a normal control; and (D) significant amyloid deposition (warm/hot colours) in a patient with clinically diagnosed Alzheimer's disease (images courtesy of AVID Radiopharmaceuticals, Inc.)