Suspecting dementia: canaries, chameleons and zebras

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ABSTRACT
The early and accurate diagnosis of dementia is more important than ever before but remains challenging. Dementia is increasingly the business of neurologists and, with ageing populations worldwide, will become even more so in the future. Here we outline a practical, symptom-led, bedside approach to suspecting dementia and its likely diagnosis, inspired by clinical experience and based on recognition of characteristic syndromic patterns. We show how clinical intuition reflects underlying signature profiles of brain involvement by the diseases that cause dementia and suggest next steps that can be taken to define the diagnosis. We propose ‘canaries’ that provide an early warning signal of emerging dementia and highlight the ‘chameleons’ that disguise or mimic this, as well as the ‘zebras’ that herald a rare (and sometimes curable) diagnostic opportunity.

INTRODUCTION
As the number of people worldwide with dementia approaches 50 million, the need for early and accurate diagnosis is more urgent than ever.1 Timely diagnosis avoids the limbo of diagnostic uncertainty and futile cycles of investigation, equips patients and families to engage appropriate support and to plan for the future, and directs rational and appropriate management.2 It will also be essential for the effective deployment of disease-modifying therapies that are on the horizon. However, the early diagnosis of dementia is challenging and remains peculiarly reliant on clinical judgement (box 1); the target diseases are complex and affect aspects of higher brain function that are generally not assessed in routine neurological practice. Treatises on dementia conventionally list the clinical features of particular diseases—in the trenches, however, the biggest challenge is often suspecting dementia in the first place and deciding why this is not ‘just’ Alzheimer’s disease.

Dementia is a syndrome that can be defined very generally as a progressive decline in cognitive function and/or behaviour that impacts daily life functioning. As such, it has a multiplicity of causes. Most of these are neurodegenerative pathologies that are not presently reversible; however, the rare exceptions are not to be missed. A key theme in dementia (especially in neurodegenerative disease) is that the causative pathologies initially target certain brain functions relatively selectively, due to a predilection of pathogenic proteins to involve particular brain networks.3 Over time, these signature patterns become obscured as the spread of pathological change leads to convergent, widespread damage and impairment. The window of greatest opportunity for accurate diagnosis (and anticipated interventions) is therefore early-stage disease. Appreciating how profiles of brain damage relate to cognitive deficits is key to deciding which diseases are likely in patients presenting with suspected dementia.

Here we outline a symptom-led, bedside approach to suspecting dementia that we have found useful in busy neurological clinics. First, we consider clues that help one decide whether or not cognitive decline is present and, if so, the likely cause. We show how these clues predictably reflect underlying signature patterns of brain involvement by causative pathologies and suggest next steps that can be taken to define the diagnosis. As with many other disorders, the neurologist’s essential task is to identify ‘canaries’ that provide an early warning signal of emerging disease, avoid being misled by ‘chameleons’ that disguise or mimic this and remain alert to the occasional ‘zebra’ that heralds a rare (and sometimes curable) diagnosis.

We suggest some general principles and tools for cognitive assessment in box 1 and
How to do it

Box 1  Some principles of bedside cognitive assessment

History taking

- History is the most important aspect of successful dementia diagnosis.
- Obtaining a history from reliable informants who know the patient well is integral and interviewing them separately may encourage sharing of sensitive or embarrassing clues to the diagnosis.
- A minute or two spent putting the patient and family at ease is well invested.
- How organised and detailed patients seem when describing their symptoms is informative, particularly if at odds with performance on formal cognitive tests.
- Interpretation of cognitive or behavioural changes depends on an appreciation of the patient’s sociocultural background, education, occupation, premorbid language skills, any pre-existing specific developmental or other deficits, and medical and psychiatric history (including medications).
- Cognitive concerns will most frequently be framed as a non-specific ‘memory’ problem: this is the most ubiquitous of several potential ‘pitfall’ symptoms that must be deconstructed (see table 2).
- Domains of cognitive function and behaviour that may not be volunteered should also be explored (as these help define the cognitive profile), framing these as questions about functioning in daily life.
- Particularly in younger people, a detailed family history is essential (including parents’ diagnoses and age at death if relevant, and the ages of any siblings).

Examination

- It is first essential to establish that the patient is alert and cooperative and that their peripheral vision and hearing are adequate (or corrected as appropriate).
- Observing the patient’s conduct and interaction with the examiner and others is often telling (it may point to frontal lobe dysfunction more clearly than any test; see table 2).
- To corroborate the history and to build a diagnostic profile of cognitive deficits, it is helpful to have a scheme for testing cognition (a ‘walk around the brain’, table 1), armed with some tools to elicit cognitive deficits (figure 1): the cognitive profile in turn predicts the underlying pattern of brain involvement (figure 2).
- Quantitative cognitive assessments such as the Mini-Mental State Examination, the Montreal Cognitive Assessment and Addenbrooke’s Cognitive Examination are widely available; however, each has its limitations and none in itself should be used to diagnose or exclude dementia.
- The general neurological and systemic examinations are essential, particularly for substantiating diagnoses other than Alzheimer’s disease (see tables 3 and 4).

figure 1 and outline a bedside framework for cognitive history taking and examination in table 1. Diagnostic canaries based on characteristic patterns of cerebral involvement are listed in table 1; potential pitfalls are listed in table 2, chameleons in table 3 and zebras in table 4.

DOES THIS PATIENT HAVE DEMENTIA?

Distinguishing early dementia from the ‘worried well’ or a ‘functional’ cognitive disorder is an increasingly frequent challenge faced by neurologists as public awareness and anxiety about dementia continue to increase. A functional cognitive disorder should be considered if there are positive features of internal inconsistency, that is, ability to perform a task well at certain times, but with significant difficulty when it becomes the focus of attention. The person who gives a detailed (or even overinclusive) account of their memory lapses, attributes their difficulties eloquently to specific past events and who is substantially more concerned about their cognitive function than their partner, children or colleagues—often attending clinic unaccompanied—is more likely to be anxious or to have a functional cognitive disorder than dementia. People with obsessional personalities are more prone to overinterpret the imperfections of normal memory. There is often a flavour of wavering concentration, such as being unable to remember why one has entered a room, misplacing household items in odd locations (eg, keys in the fridge) or ‘going blank’ during a conversation only to have the required information re-emerge soon afterward. Cognitive testing frequently generates considerable anxiety, inducing ‘thought-blocking’ and performance may vary widely between assessments, often leading to marked inconsistencies (disastrous test scores despite evident competence in daily life). This contrasts with the ‘face-saving’, humour and minimisation often seen in Alzheimer’s disease, or indifference in diseases where insight is impaired. However, particularly in older patients, functional cognitive impairment may signal an emerging neurodegenerative process which declares itself subsequently.

Depression or other primary psychiatric diagnoses must not be overlooked—these are potentially treatable and undetected carry significant risk of harm. There is often a history of previous psychiatric episodes, though this may not be volunteered. Core depressive symptoms are low mood or anhedonia, variably accompanied by fatigue, psychomotor retardation, impaired concentration, a sense of personal worthlessness, significant change in appetite or recurrent morbid thoughts. Depressed patients are often downcast and disengaged, giving frequent ‘don’t know’ responses. Active psychosis also leads to poor engagement, and there may be evidence of delusional thinking or verbal hallucinations. It is important to keep in mind that anxiety, mood changes and psychosis occur not uncommonly in ‘organic’ dementias and may be early features; moreover, organic deficits may be elaborated by patients with abnormal illness behaviour, and certain syndromes (such as parietal presentations of Alzheimer’s...
How to do it
disease and behavioural variant frontotemporal dementia) are notoriously prone to psychiatric mislabelling even by experienced clinicians.

**SOME IMPORTANT CANARIES**

**Alzheimer’s disease**
Older patients with episodic and topographical memory impairment that declines over time will most commonly have emerging Alzheimer’s disease. Details of important events and conversations are not retained, questions become repetitive and there is often a loss of facility with route-finding and a history of becoming lost. There may be a signal ‘catastrophic’ episode (often, disorientation in unfamiliar surroundings, e.g. while on holiday) preceding more pervasive deterioration. Difficulty following conversations in background noise and dislike of noisy environments (due to impaired auditory scene processing) tend to develop early. Loss of pleasure in reading (probably multifactorial in nature) is also frequently reported. Retained (partial) awareness of limitations as well as endogenous emotional changes wrought by the disease often lead to loss of confidence or initiative, embarrassment, anxiety and withdrawal from social activities, manifesting in the clinic as a tendency to ‘trail’ the accompanying person into the room and to turn to them (‘head-turning sign’) when asked a question. On bedside testing, the extent to which cognitive impairment has been masked by a well-preserved social façade may be surprising: knowledge of current affairs tends to be vague, recall of previously presented items does not benefit from cueing and topographical material (such as reconstructing the journey to the hospital) may be notably affected.

Beyond memory, parietal cortical functions including word retrieval, praxis, calculation and visuospatial function are affected relatively early in Alzheimer’s disease. There may be difficulties with word finding, handling household appliances, managing money or visuospatially demanding activities such as driving or do-it-yourself. Coming to grips with new technology taxes learning, executive and parietal functions and is often particularly challenging.

**Dementia with Lewy bodies**
Dementia commonly develops in Parkinson’s disease (particularly in older patients) and is a core feature of Lewy body pathology. Clues include an early predisposition to severe, prolonged delirium (for example, attending a minor infection or surgical procedure) and sometimes acting out of dream content (REM sleep behaviour disorder, due to loss of normal skeletal muscle atonia). Later, misperceptions and hallucinations (usually predominately visual) develop, though these may not be volunteered. Initially, they may be brief transients glimpsed in the periphery but evolve into vivid, animate entities (commonly faces, people or animals) that emerge out of background features (such as foliage or a pile of clothes) in stereotyped fashion, particularly under low-light conditions. In contrast to psychotic or dopamine-driven hallucinations, these are typically non-threatening though insight into their nature may be impaired. An ‘extracampine’
# How to do it

Table 1  Bedside assessment of the patient with suspected dementia: a ‘walk around the cognitive brain’

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Leading or early symptoms</th>
<th>Associated symptoms</th>
<th>Examination findings</th>
<th>Brain region(s)</th>
<th>First thoughts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behaviour (social and emotional)</strong></td>
<td>Loss of empathy/emotional awareness (eg, family events such as funerals, illnesses and warmth toward children/pets) and self-centredness</td>
<td>Disinhibition, loss of initiative, obsessiornality/rituals (eg, clock watching, gluttony/sweet tooth/food faddism, altered interests/humour, loss of insight/anosognosia)</td>
<td>Impulsive, inert, disinhibited interaction, 1000-yard stare'</td>
<td>Frontal lobe (especially right), right temporal lobe, other</td>
<td>Behavioural variant frontotemporal dementia</td>
</tr>
<tr>
<td></td>
<td>Irritability, more anxious and ‘clingy’</td>
<td>Quieter in social situations</td>
<td>Diffident/ head turning</td>
<td></td>
<td>Alzheimer’s disease*</td>
</tr>
<tr>
<td><strong>Language output (speech sounds, sentences and prosody)</strong></td>
<td>Stumbling over words, especially public speaking</td>
<td>Mixing up ‘yes/no’, mispronunciations, monotonous/ odd accent, grammatical/spelling slips</td>
<td>Effortful speech, reduced articulatory agility (repeating syllable strings, eg, ‘puh-kuh-tuh’), impaired repeating single words and following complex commands</td>
<td>Left inferior frontal gyrus/ peri-Sylvian</td>
<td>Non-fluent primary progressive aphasia</td>
</tr>
<tr>
<td></td>
<td>Word-finding difficulty, losing thread of sentences</td>
<td>Reduced speech quantity, pauses</td>
<td>Reduced picture naming</td>
<td></td>
<td>Logopenic aphasia</td>
</tr>
<tr>
<td><strong>Knowledge of words (vocabulary), objects and concepts</strong></td>
<td>Forgetting names, circumlocutions, vague expressing thoughts and ‘going dead’</td>
<td>Asking meaning of words, keeping personal ‘dictionaries’ and decline in spelling/understanding written words</td>
<td>Reduced knowledge of specialist vocabulary, reduced naming of objects/ability to identify pictures/define words named by examiner; surface dyslexia (irregular words, eg, ‘yacht’)</td>
<td>Left anteroinferior temporal lobe</td>
<td>Semantic primary progressive aphasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difficulty choosing groceries/tools, etc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reading, spelling and calculation</strong></td>
<td>Loss of pleasure reading Less numerical facility (eg, change)</td>
<td>Losing place reading text, difficulty resolving closely spaced text and decline in spelling ability</td>
<td>Difficulty reading blocked text and acaculca on simple mental arithmetic</td>
<td>Left parietal lobe</td>
<td>Posterior cortical atrophy, logopenic aphasia and Alzheimer’s disease</td>
</tr>
<tr>
<td><strong>Working memory (verbal)</strong></td>
<td>Poor ‘concentration’</td>
<td>Difficulty holding information for example, a new phone number in mind</td>
<td>Reduced forward (passive) digit span, reduced reverse (active) digit span and reduced repetition of phrases more than words</td>
<td>Left temporoparietal junction/frontal lobe</td>
<td>Logopenic aphasia and Alzheimer’s disease</td>
</tr>
<tr>
<td><strong>Action (learnt/ voluntary: praxis)</strong></td>
<td>Difficulty learning new devices, loss of facility with do-it-yourself, etc</td>
<td>Difficulty using household gadgets</td>
<td>Ideomotor limb apraxia: impaired copying meaningless/sequential gestures (Luria), ideational limb apraxia: impaired pantomime of learnt actions (eg, tool, waving)</td>
<td>Left parietal lobe</td>
<td>Posterior cortical atrophy and corticobasal syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difficulty positioning self in space</td>
<td>Bottom apraxia (difficulty sitting on chair)</td>
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<tr>
<td><strong>Object analysis (visual)</strong></td>
<td>Difficulty reading large/ unusual leg (eg, pixelated/CAPTCHA font; not confident on escalators; often multiple optician visits)</td>
<td>Difficulty interpreting complex scenes with patterns, over laid objects, identifying slo ped/ steps, etc; difficulty recognising or misrecognising objects in suboptimal viewing conditions</td>
<td>Difficulty perceiving fragmented letters/pictures, distorted views</td>
<td>Right parietal lobe</td>
<td>Posterior cortical atrophy and dementia with Lewy bodies</td>
</tr>
<tr>
<td><strong>Spatial awareness (visual)</strong></td>
<td>Bumps/scrapes in car, difficulty parking and difficulty filling forms, etc</td>
<td>Unable to find items in an array, placing items too close to table edge</td>
<td>Difficulty drawing clock face/copying design/counting dots, finding examiner’s outstretched hand (visual disorientation)</td>
<td>Right parietal lobe</td>
<td>Posterior cortical atrophy and Alzheimer’s disease</td>
</tr>
<tr>
<td><strong>Perception (early sensory–visual, auditory, somatic and interceptive)</strong></td>
<td>Difficulty driving if night-time/raining</td>
<td>Abnormally prolonged after-images (colour ‘washes’, often red/green), visual ‘tilt’ and other distortions</td>
<td>Impaired colour/shape discrimination (eg, oblong vs square)</td>
<td>Sensory cortices/thalamus‡</td>
<td>Posterior cortical atrophy, ‘visual’ Creutzfeldt-Jakob disease</td>
</tr>
<tr>
<td></td>
<td>‘Double vision’, brief misperceptions</td>
<td>Illusions/hallucinations</td>
<td>Check visual acuity</td>
<td></td>
<td>Dementia with Lewy bodies</td>
</tr>
<tr>
<td></td>
<td>Dislikes noisy environments</td>
<td>Difficulty conversing in noise</td>
<td>Check peripheral hearing</td>
<td></td>
<td>Alzheimer’s disease and variants</td>
</tr>
<tr>
<td></td>
<td>Tinnitus/hyperacousis</td>
<td>Altered pain/temperature awareness</td>
<td>Check basic sensory function</td>
<td></td>
<td>Semantic primary progressive aphasia and behavioural variant frontotemporal dementia</td>
</tr>
</tbody>
</table>

Continued
The most common cognitive syndrome of cerebrovascular disease is not the stepwise decline in function of classical teaching, but an insidious deterioration characterised by disorganisation, loss of vace and initiative, irritability, mental rigidity, emotional lability and other mood changes, and sometimes inappropriate or disinhibited social behaviour. Vascular risk factors are common, but their absence does not exclude the diagnosis. Examination typically reveals cognitive and affective blunting, executive dysfunction, impaired attention and recall (which in contrast to Alzheimer’s disease, does generally benefit from cueing) with variable additional, more focal deficits; however these may be over-estimated due to little evidence to the contrary.

### Vascular cognitive impairment

The most common cognitive syndrome of cerebrovascular disease is not the stepwise decline in function of classical teaching, but an insidious deterioration characterised by disorganisation, loss of vace and initiative, irritability, mental rigidity, emotional lability and other mood changes, and sometimes inappropriate or disinhibited social behaviour. Vascular risk factors are common, but their absence does not exclude the diagnosis. Examination typically reveals cognitive and affective blunting, executive dysfunction, impaired attention and recall (which in contrast to Alzheimer’s disease, does generally benefit from cueing) with variable additional, more focal deficits; however these may be over-estimated due to little evidence to the contrary.

### Some chameleons and zebras

**Alzheimer’s disease variants**

Atypical presentations of Alzheimer’s disease dominated by non-amnestic deficits are not uncommon, particularly in younger people; conversely, Alzheimer’s disease is simulated by a variety of other disease processes. Table 3 summarises some of these chameleons; it is particularly important to consider potentially reversible mimics, such as transient epileptic amnesia or obstructive sleep apnoea. There are three major Alzheimer variant syndromes, likely reflecting differential involvement of the same core tempo–parieto–frontal brain network targeted by Alzheimer pathology (see tables 1 and 2, and figure 2). These variants lie on a clinical continuum and overlap is frequent.

### Table 1 Continued

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Leading or early symptoms</th>
<th>Associated symptoms</th>
<th>Examination findings</th>
<th>Brain region(s)</th>
<th>First thoughts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face recognition</td>
<td>Loss of facility recognising faces</td>
<td>‘Blanking’ familiar people and misidentification of ‘impostors’</td>
<td>Impaired famous face recognition**</td>
<td>Right anteroinferior temporal lobe and connections</td>
<td>Semantic primary progressive aphasia and right temporal lobe atrophy††</td>
</tr>
<tr>
<td>Executive function</td>
<td>Disorganised, distractible, poor planning/decision making/multitasking/prioritising, apathetic</td>
<td>Difficulty with inference/abstraction, choosing alternatives, envisaging/learning from consequences and dealing with novelty</td>
<td>Reduced/bizarre verbal fluency (category/letter–number of animals/5’5 words in 1 min),‡‡ Stroop task errors, concrete proverb interpretation, inaccurate cognitive estimates (eg: ‘How many lions in Belgium?’§§¶¶)</td>
<td>Bilateral frontal lobe and connections</td>
<td>May be behavioural variant frontotemporal dementia but depends on associated problems</td>
</tr>
<tr>
<td>Memory (episodic and topographical)</td>
<td>More repetitive and less facility with route finding</td>
<td>Vague knowledge of current affairs and getting lost</td>
<td>Orientation to date/time/place, details of hospital journey/stay and incidental recall of pictures from naming test</td>
<td>Hippocampi and connections</td>
<td>Alzheimer’s disease (but beware)</td>
</tr>
<tr>
<td>Forgetful, absent-minded</td>
<td>Poor concentration, disorganised</td>
<td></td>
<td>Improves on cueing/foils; ‘Did you see a…?’</td>
<td></td>
<td>Vascular/other</td>
</tr>
</tbody>
</table>

This table presents early symptoms (‘canaries’; see also table 2) that signal difficulty in each major cognitive domain, together with associated symptoms that may be elicited on history. For each domain, we suggest bedside tests (see also box 1) and features that may be used to corroborate the historical impression and indicate major neuroanatomical associations (see also figure 2) and leading diagnostic considerations.

*Refers to the clinical syndrome of typical (memory-led) Alzheimer’s disease.
†Prosody/ singing may be additionally linked to right peri-Sylvian cortical regions.
‡Initial loss of knowledge of lower-frequency words reflecting patient’s interests/occupation.
§§May indicate visual agnosia (the patient with apraxia recognises how an object is used).
¶¶Dependent on education and culture.
††Refers to the syndrome associated with right temporal lobe atrophy, within the behavioural variant frontotemporal dementia spectrum.
†‡In non-aphasic patients.
†††The manner in which the patient approaches executive tests is also informative, for example, are they impulsive? do they produce odd items on fluency tests? do they produce overprecise, incorrect estimates that they cannot revise? etc.

sense of a presence beyond the field of vision is common. Marked fluctuations in alertness, attention and cognitive competence even within the course of a day (particularly deterioration later in the day) are also characteristic. Complaints of ‘double vision’ and problems reading (without identifiable ocular pathology) are common, and difficulty using gadgets such as a smartphone exposes executive and parietal dysfunction. Features of associated Parkinsonism (such as hypomimia or gait changes) may be subtle initially but it is worth asking about autonomic symptoms (particularly urinary urgency, nocturia or unexplained collapses).
Table 2  Some noteworthy potential ‘pitfall’ symptoms and signs requiring further clarification or interpretation in suspected dementia

<table>
<thead>
<tr>
<th>Feature</th>
<th>Clarification/interpretation</th>
<th>Major causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambiguous symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘Poor memory’</td>
<td>Often used as a shorthand for ‘cognitive problem’, does it mean episodic memory (events, routes, conversations, etc), semantic memory (words and concepts) or another domain of cognition? If the issue is with memory, is it with encoding information (attention), retaining new information (anterograde memory) or retrieving old information?</td>
<td>Any (may have poor episodic memory in dementia with Lewy bodies, frontotemporal dementia, etc, as well as Alzheimer’s disease*)</td>
</tr>
<tr>
<td>‘Getting lost’</td>
<td>Is this truly difficulty completing a route without assistance (topographical disorientation) or wandering (but ultimately getting there)? A useful question can be ‘how would you make your way home from here if you had to do it alone’?</td>
<td>Alzheimer’s disease (topography) and behavioural variant frontotemporal dementia (wandering)</td>
</tr>
<tr>
<td>‘Word-finding difficulty’</td>
<td>Often used as a shorthand for ‘language problem’; is it difficulty retrieving the name (very common), loss of vocabulary or difficulty pronouncing the word (uncommon)?</td>
<td>Alzheimer’s disease/other (retrieval), semantic primary progressive aphasia (vocabulary) and non-fluent primary progressive aphasia (articulation)</td>
</tr>
<tr>
<td>‘Lost interest in reading’</td>
<td>Is this a general loss of concentration or initiative, anhedonia, difficulty following the plot or a more specific problem tracking lines of text?</td>
<td>Alzheimer’s disease (multifactorial) and posterior cortical atrophy (text tracking)</td>
</tr>
<tr>
<td>‘Doesn’t recognise people’</td>
<td>Is this inability to recall their name (personal anoma, common) or to recognise faces or voices, ‘blanking’ familiar people? (true prosopagnosia or phonagnosia, uncommon)</td>
<td>Alzheimer’s/other (names), semantic primary progressive aphasia/right temporal lobe atrophy (familiarity)</td>
</tr>
<tr>
<td>‘More anxious/irritable’</td>
<td>Might be psychiatric (eg, atypical depression) but also an early feature of many ‘organic’ dementias</td>
<td>Alzheimer’s disease, dementia with Lewy bodies, vascular and some frontotemporal dementias (eg, C9orf72 mutations)</td>
</tr>
<tr>
<td>‘Black sheep of family’</td>
<td>Youthful delinquency that contrasts with law-abiding siblings</td>
<td>Latent learning disability, very rarely genetic prion disease</td>
</tr>
<tr>
<td><strong>Counterintuitive symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘Asks meaning of words’</td>
<td>Loss of ability to understand words in a familiar language</td>
<td>Semantic primary progressive aphasia</td>
</tr>
<tr>
<td>‘Reads fine print but not the headlines’</td>
<td>Visual apperceptive agnosia exposed by non-canonical (eg, very large or pixelated) text</td>
<td>Posterior cortical atrophy</td>
</tr>
<tr>
<td>‘Can play tennis (etc) but can’t find ball on ground’</td>
<td>Static visual localisation more impaired than motion vision (or occasionally the reverse), reflecting separable neuroanatomical substrates</td>
<td>Posterior cortical atrophy</td>
</tr>
<tr>
<td>‘Says spouse is impostor’</td>
<td>Misidentification delusion (Capgras, etc), can also be for location (eg, asks to go ‘home’ in own house)</td>
<td>Alzheimer’s disease, dementia with Lewy bodies</td>
</tr>
<tr>
<td>‘Much nastier/nicer now’</td>
<td>Altered interpersonal awareness and conduct</td>
<td>Behavioural variant frontotemporal dementia (nasty) and Alzheimer’s disease (nice)</td>
</tr>
<tr>
<td>‘Become very musical/religious/punctual/good at Sudoku’</td>
<td>Enhanced (sometimes loss of) interest/ability in abstract pursuits, usually with loss of interest/affection for other people, on a spectrum of alterations ranging from basic rewards (sweet food and sleep), through sense of humour and timekeeping, to puzzles/complex stimuli</td>
<td>Behavioural variant frontotemporal dementia and semantic primary progressive aphasia</td>
</tr>
<tr>
<td><strong>Potentially misleading symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘It all started after that… (accident/operation, etc)’</td>
<td>Usually, this is attribution bias; occasionally we have seen cases where severe psychological trauma did seem to provoke catastrophic cognitive decline in a previously asymptomatic person</td>
<td>Any</td>
</tr>
<tr>
<td>‘Distant memories are fine’</td>
<td>Usually they are not, but highly overlearnt or emotional memories tend to become the focus of cherished anecdote</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>‘Poor short-term memory’</td>
<td>To a neuropsychologist, this refers to the immediate span of working memory (up to ~30s) but used colloquially to refer to recent episodic memory of variable span</td>
<td>Any</td>
</tr>
<tr>
<td>‘Thinks people are stealing from them’</td>
<td>Usually not a harbinger of psychosis but a specific delusion of theft (or infidelity)</td>
<td>Alzheimer’s disease, dementia with Lewy bodies</td>
</tr>
<tr>
<td>‘Going deaf’</td>
<td>Peripheral hearing should always be checked but in context may signify difficulty understanding word meaning</td>
<td>Semantic primary progressive aphasia</td>
</tr>
<tr>
<td>‘Always been spiritual’</td>
<td>Apparent receptivity to ‘ghosts’/presences may signify visual/extracampine hallucinations</td>
<td>Dementia with Lewy bodies</td>
</tr>
<tr>
<td>‘Unexplained aches/pains’</td>
<td>Hypochondriasis can occasionally reflect abnormal processing of interoceptive signals such as pain</td>
<td>Right temporal lobe atrophy and semantic primary progressive aphasia</td>
</tr>
</tbody>
</table>

Continued
Posterior cortical atrophy, the ‘visual variant’ of Alzheimer’s disease, usually presents with impairments of visuospatial awareness, reading and praxis.17 Beware the patient whose disease, usually presents with impairments of visuo-examination, impaired repetition of phrases despite intact sensory acuity. There is usually a full hand of clues to the diagnosis.26

Dysprosodia (isolated) Most cases of ‘foreign accent syndrome’ (recognisable as such, sometimes simulated with pantomime exuberance) will be functional, but occasionally patients present with altered prosody and linguistic deficits only supervene (much) later

Executive dysfunction As used, for example, in neuropsychological reports, it is not synonymous with ‘frontal lobe problem’ but reflects processing across distributed brain networks; moreover, patients with significant frontal lobe dysfunction (as reflected in abnormal behaviour) may perform well on executive tests

Signs not to miss/misinterpret

<table>
<thead>
<tr>
<th>Feature</th>
<th>Clarification/interpretation</th>
<th>Major causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottom apraxia</td>
<td>Difficulty orienting/positioning self in space as when sitting down in a chair</td>
<td>Posterior cortical atrophy and corticobasal syndrome</td>
</tr>
<tr>
<td>Closing in</td>
<td>Patients overlay their hand or drawing on examiner’s target—feature of organic apraxia</td>
<td>Alzheimer’s disease and posterior cortical atrophy</td>
</tr>
<tr>
<td>‘(Vicar of) Dibley’ sign</td>
<td>Binary reversals during conversation—says ‘yes’ but means ‘no’, etc</td>
<td>Non-fluent primary progressive aphasia</td>
</tr>
<tr>
<td>Dysprosodia (isolated)</td>
<td>Most cases of ‘foreign accent syndrome’ (recognisable as such, but occasionally patients present with altered prosody and linguistic deficits only supervene (much) later</td>
<td>Non-fluent primary progressive aphasia</td>
</tr>
<tr>
<td>Executive dysfunction</td>
<td>As used, for example, in neuropsychological reports, it is not synonymous with ‘frontal lobe problem’ but reflects processing across distributed brain networks; moreover, patients with significant frontal lobe dysfunction (as reflected in abnormal behaviour) may perform well on executive tests</td>
<td>Any</td>
</tr>
</tbody>
</table>

Dementia with Lewy bodies (sleep benefit), transient epileptic amnesia (sleep deterioration), inflammatory, immune

*Refers to the clinical syndrome of typical (memory-led) Alzheimer’s disease.
†Refers to the syndrome associated with right temporal lobe atrophy, within the behavioural variant frontotemporal dementia spectrum.
‡Not the same as inconsistency—organic cognitive fluctuations are internally consistent.

Posterior cortical atrophy, the ‘visual variant’ of Alzheimer’s disease, usually presents with impairments of visuospatial awareness, reading and praxis.17 Beware the patient who has made numerous futile visits to the optician or who describes more difficulty reading pixelated signs than newsprint (signifying visual apperceptive agnosia): this is the cardinal degenerative disorder of the visual brain, disrupting the interpretation of visual scenes despite normal sensory acuity. There is usually a full hand of accompanying parietal lobe deficits, but episodic memory early on is often well preserved.

Logopenic aphasia is the language-led variant of Alzheimer’s disease within the primary progressive aphasia spectrum.25 It is characterised by prominent word-finding difficulty, conversational pauses (sentences tend to trail off) with speech sound (phonological) errors and, on examination, impaired repetition of phrases despite intact repetition of single words (due to reduced verbal working memory).26

The ‘frontal’ (behavioural/dysexecutive) variant of Alzheimer’s disease remains the least well defined.27 Clinically, it can closely resemble the behavioural variant of frontotemporal dementia, but prominent accompanying memory impairment and confabulation may be bedside clues to the diagnosis.

**Frontotemporal dementia syndromes**

Among the ‘zebras’ of dementia diagnosis, the frontotemporal dementias are particularly important because they are collectively a major cause of dementia in middle life and wreak havoc on social and occupational functioning. This is a diverse group of diseases with complex neurobiology28; however, three major clinical presentations are recognised.
### Table 3  Some important ‘chameleons’ of dementia diagnosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chameleons</th>
<th>Some useful features to identify the chameleon</th>
</tr>
</thead>
</table>
| Alzheimer’s disease                        | Mimics *  
Transient epileptic amnesia†  
Obstructive sleep apnoea†  
Normal-pressure hydrocephalus†  
Vascular  
Traumatic brain injury/chronic traumatic encephalopathy  
Dementia with Lewy bodies  
Dementia and other neurodegenerative disorders  
Variants  
Posterior cortical atrophy  
Logopenic aphasia  
Behavioural variant frontotemporal-like  
Corticobasal syndrome  
Young onset (sporadic)  
Rapid (may have beta-amyloid angiitis)  
Familial  
Dementia with Lewy bodies  
Dementia and other neurodegenerative disorders  
Dementia with Lewy bodies  
Dementia and other neurodegenerative disorders  |
|                | Clinical seizures (not invariable), prominent fluctuation, ‘vacational’ amnesia†; abnormal (extended) EEG, may have other features of limbic encephalitis, auto-antibodies / cancer  
Daytime somnolence, non-refreshing sleep, heavy snoring (from partner); abnormal sleep study  
May have gait apraxia, urinary dysfunction; MRI hydrocephalus and associated features  
MRI: strategic (eg, thalamic) infarct, other vascular patterns (including deep micro- haemorrhages)  
History of significant (especially recurrent) head trauma  
Varied according to underlying pathology; may have genetic mutation (frontotemporal dementia, familial prion), some entities (eg, argyrophilic grain disease, limbic-predominant age-related TDP-43 encephalopathy) currently only diagnosed post mortem  
Positive Alzheimer markers in CSF (raised total / phospho-tau, reduced beta-amyloid42 and beta-amyloid42/40 ratio), cortical micro- haemorrhages associated with amyloid angiopathy  
Positive Alzheimer CSF and MRI markers, cortical micro- haemorrhages/siderosis on MRI  
Young, autosomal dominant family history (may be censored); may have spastic para- paraparesis/other neurological signs (especially PS1 mutations), prominent neuropsychiatric features, white matter change on MRI; PS1, PS2 or APP mutation (in addition to Alzheimer CSF markers) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Dementia with Lewy bodies                   | Mimics  
Progressive supranuclear palsy and corticobasal syndrome  
Variants  
Alzheimer-like  
Behavioural variant frontotemporal-like  
Rapid  | Supranuclear gaze palsy, prominent asymmetric apraxia/axial rigidity; poor levodopa response  
Flord delirium, prominent fluctuations, early visual hallucinations, REM sleep behaviour disorder, emerging parkinsonism |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Vascular cognitive impairment               | Mimics  
Infectious/inflammatory/autoimmune†  
Genetic arteriopathies  
Primary leukodystrophies  
Variants  
Behavioural variant frontotemporal-like  
Prominent amnestic/focal ‘cortical’ deficits  | Suggestive history, autoantibodies, blood/CSF serology (eg, human immunodeficiency virus and syphilis)  
Young, lack of vascular risk factors, suggestive family history; migraine, psychiatric features, MRI involvement of anterior temporal lobe, NOTCH3 mutations with CADASIL  
Young, lack of vascular risk factors, suggestive MRI (confluent, symmetric white matter change), positive diagnostic tests  
MRI: significant vascular change, lack of suggestive atrophy profile  
MRI: strategic infarct (especially thalamic, parietal) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Frontotemporal dementia†                   | Mimics  
‘Frontotemporal dementia phenocopy’ (especially older men)  
Frontal variant of Alzheimer’s disease  
Vascular  
Dementia with Lewy bodies  
Variants  
Amnestic/Alzheimer-like  
Corticobasal syndrome  
Motor neurone disease  
Very young onset/rapid  | Normal brain MRI/ fluorodeoxyglucose-PET; some frontotemporal dementia cases (especially C9orf72 mutations) may be very slowly progressive—phenocopy cases often show better preserved insight than is usual with frontotemporal dementia  
Prominent associated episodic memory deficit, relatively prominent posterior atrophy on MRI, Alzheimer biomarkers (CSF, amyloid PET)  
MRI: vascular features  
Visual hallucinations, REM sleep behaviour disorder  
Negative Alzheimer biomarkers  
May have GRN mutation  
May have C9orf72 mutations  
MRI: disproportionate caudate atrophy (FUP-opathy) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

*Here, chameleons are either ‘mimics’—a different disease that presents similarly to the typical syndrome, listed in the left-most column—or ‘variants’—an alternative, atypical presentation of the same disease process that causes the typical syndrome.  
*Negative Alzheimer markers may be helpful but Alzheimer pathology frequently coexists with other entities (seizures, obstructive sleep apnoea more common in Alzheimer’s disease).  
†Potentially reversible process.  
‡No recollection at all of salient events such as vacations (typically in Alzheimer’s disease, there is some recollection of the episode, although degraded).  
§Presentation with behavioural variant here taken to be typical (clinical mimics of primary progressive aphasia syndromes are very uncommon).  
APP, amyloid precursor protein; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; C9orf72, mutation of chromosome 9 open reading frame 72; CSF, cerebrospinal fluid; EEG, electroencephalogram; FUS, fused-in-sarcoma protein; GRN, progranulin gene; NOTCH3, neurogenic locus notch homolog protein 3 mutations; PET, positron emission tomography; PS1, presenilin 1 gene mutation; PS2, presenilin 2 gene mutation.
### Table 4  Some important ‘zebras’ in dementia diagnosis

<table>
<thead>
<tr>
<th>Leading clue</th>
<th>Syndromic features (especially early)</th>
<th>Candidate diagnoses</th>
<th>Key investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unusual</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socioemotional decline leading</td>
<td>Reduced empathy, disinhibition, apathy, obsessiolonality, stereotypes, altered eating behaviour, executive deficits; atypical parkinsonism (progressive supranuclear palsy/corticobasal syndrome) frequent later</td>
<td>Behavioural variant frontotemporal dementia</td>
<td>MRI (figure 2), but atrophy highly variable and may be subtle; may have associated midbrain atrophy (progressive supranuclear palsy), genetics</td>
</tr>
<tr>
<td>Language decline leading</td>
<td>Effortful, misarticulated, apraxic speech, binary reversals, grammatical errors, otorofacial apraxia, atypical parkinsonism (progressive supranuclear palsy/corticobasal syndrome) frequent later</td>
<td>Non-fluent primary progressive aphasia</td>
<td>MRI (figure 2), but atrophy variable; genetics if young/suspicious family history</td>
</tr>
<tr>
<td></td>
<td>Loss of vocabulary, severe anoma with impaired single word comprehension despite fluent well-structured speech, often frontotemporal dementia-like behaviours</td>
<td>Semantic primary progressive aphasia</td>
<td>MRI (figure 2) characteristic</td>
</tr>
<tr>
<td></td>
<td>Aroma/Word-finding pauses, phonemic errors, phrase repetition/ verbal working memory deficits</td>
<td>Logopenic aphasia (usually Alzheimer pathology)</td>
<td>MRI asymmetric (predominantly left-sided) temporoparietal atrophy, CSF Alzheimer markers</td>
</tr>
<tr>
<td>Visualspatial decline leading</td>
<td>Difficulty reading unusual fonts/right driving/gadgets, mispositioning items; later apraxic/hyperoragnosia/ dorsolalia, anomia</td>
<td>Posterior cortical atrophy (usually Alzheimer pathology; some dementia with Lewy bodies, others)</td>
<td>MRI (figure 2), CSF Alzheimer markers</td>
</tr>
<tr>
<td>‘Frontal’—ataxia</td>
<td>Also urinary urgency/continence May have history of prior neurological episodes History of cranial irradiation (often delayed), also pyramidal/other neurological signs</td>
<td>Normal-pressure hydrocephalus†</td>
<td>MRI ventriculomegaly and associated features</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple sclerosis (especially primary/ secondary progressive)</td>
<td>MRI (brain/cord) demyelination features, CSF unmatched oligoclonal bands</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-irradiation vasculopathy</td>
<td>MRI extensive white matter damage</td>
</tr>
<tr>
<td>Rapid‡</td>
<td>Early widespread cognitive impairment (often prominent visual dysfunctions), myoclonus/other neurological signs Frontotemporal dementia plus deltoid/triceps fasciculations, pyramidal signs Behavioural variant frontotemporal dementia-like plus corticobasal syndrome, atypical parkinsonism, young, markedly obsessive/stereotypical behaviour</td>
<td>Creutzfeldt-Jakob disease (classically, Alzheimer’s disease, dementia with Lewy bodies (uncommonly) Frontotemporal dementia—motor neuron disease C9orf72</td>
<td>MRI cortical/basal ganglia signal change, EEG (periodic complexes—Creutzfeldt-Jakob disease), CSF (RT-QuIC, Alzheimer markers), DAT (Dementia with Lewy bodies), genetics MRI, EMG (often normal), genetics MRI marked caudate atrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limbic encephalitis†</td>
<td>MRI, CT angiogram, CSF pleocytosis, autoantibodies/inflammatory markers; consider brain biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seizures, jerks, dyskinesias, fluctuation, neuropsychiatric/autoimmune/ systemic features</td>
<td>MRI high signal in hippocampal/temporal lobe, autoantibodies, whole body-PET/CT scans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Executive/behavioural decline with gait disturbance</td>
<td>variable other neurological features</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunosuppressed, compatible history of infection</td>
<td>MRI abnormal signal/gadolinium enhancement, blood/CFS serology</td>
</tr>
</tbody>
</table>

Continued
### Table 4  Continued

<table>
<thead>
<tr>
<th>Leading clue</th>
<th>Syndromic features (especially early)</th>
<th>Candidate diagnoses</th>
<th>Key investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxic exposure/dietary deficiency states</strong></td>
<td>Alcohol usually nutritional, especially thiamine (Wernicke–Korsakoff syndrome); heroin and other drug abuse, lithium toxicity, iatrogenic, metal†</td>
<td>Spinocebellar ataxias, Niemann–Pick C, fragile X, mitochondrial, dentatorubral pallidolysian atrophy, Kufs’ disease, prion</td>
<td>MRI various patterns with white/grey matter involvement, abnormal signal, drug, metabolic, metal screens</td>
</tr>
<tr>
<td><strong>Young adult,</strong> neurological</td>
<td>Ataxia</td>
<td>Paraneoplastic†, superficial siderosis</td>
<td>This group in general requires specialist consultation—principles are: (1) definition of phenotype with brain MRI, plus CSF electrophysiology, depending on presentation; (2) blood screens (metabolic/inflammatory) and/or genetics directed to cause; (3) tissue biopsy if required for diagnosis (especially muscle/axillary skin for storage diseases, etc)</td>
</tr>
<tr>
<td>Akinetic–rigid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic</td>
<td>Sarcoïdosis†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bucco/lingual mutilation</td>
<td>Antiphospholipid, rheumatological†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chore/Aldystonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deafness (peripheral)</td>
<td>Susac’s syndrome†, Behçet’s disease, superficial siderosis, sarcoidosis†</td>
<td>Mitochondrial, hereditary sensory and autonomic neuropathy 1E</td>
<td></td>
</tr>
<tr>
<td>Eye abnormalities</td>
<td>Behçet’s disease, sarcoidosis, Susac’s syndrome†</td>
<td>Cataract: cerebrotendinous xanthomatosis, myotonic dystrophy, mitochondrial</td>
<td></td>
</tr>
<tr>
<td>Gaze palsy</td>
<td>Chronic meninglides (inflammatory/ neoplastic)†</td>
<td>Gaze apraxia: Huntington’s disease</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Sarcoïdosis†</td>
<td>Mitochondrial, neuroacanthocytosis, Fabry’s,† spinocerebellar ataxia type 2, Gaucher’s†</td>
<td></td>
</tr>
<tr>
<td>Pyramidal signs</td>
<td>Poor control, anticonvulsants†</td>
<td>Mitochondrial, dentatorubral—pallidolysian atrophy, Lafora body disease, Kufs’ disease, other progressive myoclonic epilepsies</td>
<td></td>
</tr>
<tr>
<td>Seizures (especially myoclonic)</td>
<td>Antiphospholipid syndrome†</td>
<td>Cerebral amyloid angiopathies (familial), Fabry’s†</td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Hepatic encephalopathy†</td>
<td>Wilson’s disease, 1 Gaucher’s, 1 mitochondrial, porphyria†</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal abnormalities</td>
<td>Rheumatological†</td>
<td>Paget’s disease, inclusion body myopathy: VCP</td>
<td></td>
</tr>
</tbody>
</table>
The behaviour variant of frontotemporal dementia presents with abnormalities of social and emotional awareness and reactivity. The patient generally lacks insight, but the family complains bitterly that they have ‘changed’, typically with loss of warmth and social skills (there may have been embarrassing faux pas), and frequently prominent apathy, rituals and/or impulsivity that may have resulted in loss of a job or ill-advised decisions. Gluttony and development of a pathological sweet tooth are characteristic, exemplifying a much broader repertoire of odd, inflexible and maladaptive behaviours with valuation of abstract or impersonal interests over other people. These features may be particularly striking in patients with selective right temporal lobe atrophy, who also frequently exhibit prosopagnosia. Behavioural variant frontotemporal dementia is challenging to diagnose, particularly early on, as there are few reliable biomarkers. Patients may do well on formal cognitive (including executive) tests. There are several highly pertinent clinical issues surrounding the diagnosis: it is genetically mediated in up to perhaps a third of cases (genetic testing for the three major causative, autosomal dominant mutations should be considered in all younger patients) and vigilant neurological follow-up is indicated, both to detect the emergence of major associations (atypical parkinsonism or motor neurone disease) and to identify patients who fail to manifest abnormalities on brain MRI or metabolic (fluorodeoxyglucose - positron emission tomography (FDG-PET) or single-photon emission computed tomography (SPECT)) imaging. The nosological status of these latter ‘phenocopy’ cases is still unclear.

Among language-led dementia syndromes (the primary progressive aphasias), the non-fluent/agrammatic variant is the most immediately clinically striking. These patients characteristically have effortful, unmelodious, misarticulated ‘apraxic’ speech and their utterances may be terse and agrammatic (‘telegraphic’). Early on, there may be particular difficulty with public speaking, reversing of ‘yes’ and ‘no’ or re-emergence of a childhood stutter. Initially, naming and comprehension are largely intact and written expression is usually more fluent than speech. As the syndrome evolves, impairments of orofacial praxis (affecting volitional movements such as whistling) and dysphagia often supervene, frequently with emergence of an extrapyramidal syndrome in the corticobasal—progressive supranuclear palsy spectrum.

In contrast, the semantic variant of primary progressive aphasia presents with increasingly circumlocutory and vacant speech that is well constructed and fluent (even garrulous). These patients characteristically have asked family members the meanings of words (“What’s a tornado?”) and often compile personal ‘dictionaries’. They have early, profound anomia, underpinned by impaired single-word comprehension and vocabulary loss affecting all language channels, often extending to a tendency to sound irregular words (such as ‘sew’) as they are printed (‘surface dyslexia’). The true
nature of this syndrome is captured in its older designation, ‘semantic dementia’: this is the paradigmatic disorder of the semantic memory system that mediates knowledge about words, objects and concepts. As it evolves, non-verbal semantic knowledge about visual and other sensory objects and about the emotional and social signals of other people also disintegrates. Patients generally develop a behavioural syndrome similar to behavioural variant frontotemporal dementia. In our experience, there is invariably focal, asymmetric, usually predominantly left-sided anterior temporal lobe atrophy on brain MRI at presentation (figure 2); if this is absent, we hesitate to invoke the diagnosis.

Other ‘zebras’
These are many and diverse (table 4); clues to their presence include younger age of onset, a family history of younger onset dementia (often labelled as Alzheimer’s disease or psychiatric illness), prominent extracognitive neurological or systemic features or a rapid course. The last group includes catastrophic illnesses such as prion disease but also several reversible processes that demand careful exclusion (table 4). Diagnosis of the many rare diseases that cause dementia in younger adults due to metabolic, inflammatory, storage and other inherited disorders generally depends on clinical features or markers beyond cognition31 32: these disorders tend to produce a fairly nondescript ‘fronto-subcortical’ cognitive syndrome led by executive and neuropsychiatric dysfunction.

NEXT STEPS AFTER SUSPECTING DEMENTIA
If available, more detailed cognitive testing with a neuropsychologist is often a valuable extension to the bedside assessment to: quantify suspected deficits

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**Key points**

- Dementia is a syndrome of progressive decline in cognitive function and/or behaviour that impacts upon daily life functioning and has multiple potential causes.
- Timely diagnosis is desirable and achievable with a systematic approach to cognitive assessment.
- The major dementias target particular brain networks and accordingly have distinct phenotypes.
- The diagnosis rests primarily on clinical assessment, with neuropsychological, neuroimaging and biomarker support where appropriate.
in relation to age-appropriate norms and premorbid attainment; detect deficits in domains (such as executive function) that are challenging to assess at the bedside; and compare performance over serial assessments, which may be diagnostic in cases of clinical doubt.

Any patient with suspected dementia should have brain imaging (ideally MRI)—occasionally this will show a surgically remediable process but more generally it defines the profile of atrophy in neurodegenerative diseases (figure 2) and detects signal alterations such as those associated with cerebrovascular disease, leukodystrophies and prion disease. Serial imaging of change over a year or more can be informative if the first scan is normal. Conversely, frontal or parietal ‘atrophy’ is quite commonly overinterpreted on MRI. Brain FDG-PET or SPECT is sometimes useful to demonstrate regional cerebral hypometabolism where Alzheimer’s disease or a frontotemporal dementia is suspected but MRI is inconclusive.

Although basic haematological and metabolic screens are worthwhile to detect potentially reversible factors that may contribute to cognitive decline, these are rarely the primary culprit. Diagnostic markers of dementia are currently largely derived from CSF analysis, which should be considered in anyone with younger onset dementia (arbitrarily, before the age of 65 years) or rapid evolution, when it is likely to have the most useful predictive value (see tables 3 and 4)—relevant CSF constituents include cells and oligoclonal bands (pointers to brain inflammation), neurofilament light chain (a non-specific indicator of the presence and severity of neuronal damage) and more specific protein profiles of Alzheimer pathology (raised total and phospho-tau, elevated tau:beta-amyloid42 or beta-amyloid40:amyloid42 ratio).

Diagnostic testing for causative genetic mutations should be considered in younger patients where there is a compatible phenotype and in particular a suggestive (autosomal dominant) family history, but only after appropriately informed counselling in the clinic, particularly with respect to the implications for other family members. Other more specialised investigations may be appropriate in certain clinical contexts (see table 4).

Local services should be engaged for support early and people with atypical forms of Alzheimer’s disease or non-Alzheimer dementias can be directed to Rare Dementia Support (https://www.raredementiasupport.org/).

CONCLUSIONS

Early and accurate diagnosis of dementia is desirable and achievable, but it must first be suspected. As always in neurology, pattern recognition is key. The first challenge is to determine whether dementia is likely and then, based on a functionally oriented history and systematic examination, to determine the profile of cerebral involvement and thus the candidate underlying pathology. Despite a growing array of ancillary tools, clinical judgement is likely to remain essential and indeed, to assume even greater importance as effective treatments become available.

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REFERENCES


How to do it


